A PHYSICAL INTERPRETATION OF SHOCK, EXHAUSTION, AND RESTORATION

GEORGE W. CRILE

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A PHYSICAL INTERPRETATION OF SHOCK, EXHAUSTION, AND RESTORATION

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A PHYSICAL INTERPRETATION OF SHOCK, EXHAUSTION, AND RESTORATION

AN EXTENSION OF THE KINETIC THEORY

BY

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TO BARNEY

PREFACE

THE purpose of this volume is to present summaries of researches which have been in progress for many years in my laboratory and clinic in Cleveland and for two years in France during the war, and to formulate a correlative interpretation.

My grateful appreciation is due to H. M. Hanna, Esq., and to Mrs. Lee McBride for their generous interest in our research, as expressed by their support of the laboratory in Cleveland during my absence in France; to Dr. W. E. Lower for his unfailing interest and encouragement; and to Grace McB. Crile and Amy F. Rowland, whose untiring efforts made the continuation of the research in Cleveland possible during my absence in France.

The preparation of this publication was made amidst the stress of other work in France and at home, the demands of which have been imperative. Adequate reference to the work of others has, therefore, been impossible. Indeed, an adequate survey of the enormous literature in many languages which has been promulgated by the workers in the various fields with which our study has been concerned would be a large research in itself.

GEORGE W. CRILE.

CLEVELAND, OHIO, U.S.A.,
December 1920.

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INTRODUCTION

I

Exhaustion may be produced by want of food or drink or oxygen; by exposure to cold or wet; by want of sleep; by a period of excessive muscular or mental work; by a prolonged emotional strain—worry or anxiety; by defence against chronic infection and by failure to eliminate waste products. Low blood-pressure and subnormal temperature are not marked features of exhaustion.

Shock, on the other hand, is commonly caused by a more abrupt overwhelming stimulus—physical injury, intense emotion, acute infection, anaphylaxis, etc. In shock, the brain is more rapidly impaired; the power of the brain-cells to transform potential into kinetic energy is more suddenly broken; consequently the organism cannot perform its normal work—and metabolism collapses; the temperature is subnormal; there is general prostration.

In war the exhaustion of the soldier is greater in cold and rainy than in warm and dry weather; it is increased by bombing and shelling and gassing, by raiding and attacking and defending—day and night—through long stretches without relief. Exhaustion is greater when the soldier is compelled to live for days—even weeks—among the fragmented and the unburied dead. It is greater when the daily deficit of sleep is so great as to produce continuous, dull, semi-consciousness; it is greater when food is secured by scavengering and thirst is slaked with polluted water; it is greater when there is deep, heavy mud. Under such conditions a whole army becomes emaciated, sallow and weak, and many soldiers die in their tracks, die without wounds, die without disease—they die from exhaustion.

In troops thus exhausted slight injuries, slight infections, slight operations may cause death. Among the causes of a high mortality in troops which have been subjected to these conditions, the wounds may be the least important, for such soldiers may be said to be in exhaustion or in shock before the wound is received.

Every normal individual has within himself large factors of safety. If

much of the normal margin of safety is consumed before injury, then so much the more readily does the wound produce what is called *shock*. On the contrary, a soldier wounded soon after his arrival at the front, while he is still fresh, may show no immediate 'shock'—for shock appears only after the factors of safety have been consumed; just as the Marathon runner is not exhausted at the beginning, but at the end of the race. Tens and hundreds of thousands of troops *en bloc* may be in a state of chronic exhaustion or in a chronic state which predisposes to 'shock.' It may take a serious wound and the lapse of hours to reduce a fresh soldier to the 'shock' level of the battle-exhausted soldier without a wound. There is probably no ultimate difference between the exhaustion produced by the privation and stress of war and that produced by the bodily injuries of war—no ultimate difference between the *bloodless, intangible* causes of exhaustion and the *bloody, tangible* causes of shock.

Therefore, our premises in studying 'fatigue,' 'shock,' and 'exhaustion' are identical. These states have interchangeable values; they rest on some common biologic principle. When the mechanism of 'fatigue' and 'exhaustion' is understood, the mechanism of 'shock' will be understood.

As we have stated above, the term 'shock' is used to denote a state of exhaustion which has been *rapidly* developed by psychic, traumatic, toxic, or thermal stimuli. If, in the confusion of a battle, a soldier with a crushed toe limps in an imperative retreat for several days in pain and distress, in cold and mud, without food or drink or sleep, and is finally found prostrated, pulseless, semi-conscious, clammy, dying—is he in 'shock' or in 'exhaustion,' or both? What caused the condition? Was it the injury of the toe; the stress of events; or both? Who can separate one of the causative factors from the rest?

If we disregard the presence or the absence of injury, can even a complete autopsy or the most comprehensive microscopic and clinical study isolate the determining cause of death in battle? Can such a study determine whether death is the result of exposure, of cold, of fear, of worry, of loss of sleep, of struggle in mud, of injury, or of the combination of all? Neither in the living nor in the dead is there apparent any gross or any microscopic evidence that can distinguish the effects of one of these causative factors from the effects of the rest.

Even if there were such distinguishing features, they could rarely be dissociated—they could not be considered separately—since almost no case of exhaustion exists that is not the result of the combination of several factors.

In this study, therefore, we shall use the word 'exhaustion' as an inclusive term in our attempt to indicate certain limitations as well as certain values of existing clinical, experimental, and theoretical hypotheses, and to suggest new lines of attacking the problem.

II

The more recent researches reported in this volume logically follow those reported in the following volumes and partially summarised here : *Surgical Shock* (1897), *Surgery of the Respiratory System* (1899), *Certain Problems Relating to Surgical Operations* (1901), *Blood-Pressure in Surgery* (1903), *Hemorrhage and Transfusion* (1909), *Phylogenetic Association in Relation to Certain Medical Problems—Ether Day Address* (1910), *Anemia and Resuscitation* (1914), *Anoci-Association* (with Dr. W. E. Lower) (1915), *Origin and Nature of the Emotions* (1915), *The Kinetic Drive* (1916), and *Man, an Adaptive Mechanism* (1916).

During our researches, we were continually confronted by the constant coexistence of certain clinical phenomena with certain histologic changes in the brain, the liver, and the adrenals in exhaustion from various causes.

We were unable to understand the relation of these phenomena to exhaustion until it occurred to us to seek the explanation in the laws of biologic adaptation. This conception was presented in the Ether Day Address delivered at the Massachusetts General Hospital in 1910. From that time to the present we have been guided in our studies by the principles of Biologic Adaptation.

The Kinetic Theory of Shock which was evolved from these premises harmonised large groups of laboratory and clinical phenomena, and yielded the shockless operation through anoci-association.

In our more recent laboratory researches and clinical studies, we have subjected animals to every available cause of exhaustion, and in these and in normal animals we have made histologic studies of all the organs and tissues ; have made physiologic studies of the circulation, the respiration, the adrenals, and the thyroid ; have made chemical studies of the thyroid, the liver, the muscles, and the adrenals ; have measured the H-ion concentration of the blood, of the cerebro-spinal fluid, of the bile, and of the urine ; have estimated the reserve alkalinity of the blood ; have made observations on the electric conductivity of various organs and tissues ; and have made calorimetric studies.

By the same methods we have studied the effects of various means of protection and of restoration—of alkalis, of morphin, of anesthetics, of sleep.

Our findings in these studies have been related to the gross behaviour of animals in exhaustion from the same causes.

In addition we have utilised also evidence which by some observers has been held in rather low esteem—the human phenomena presented in conditions identical with or allied to those induced in the animals studied in the laboratory.

Our confidence in the relative value of the evidence presented by animal and by human behaviour rests on the fundamental fact that in the organism numerous mechanisms have been evolved to respond specifically and with the most delicate accuracy to physical and physico-chemical influences. This fact explains the value of the so-called biologic tests, which in many instances are more delicately accurate than the artificial tests of the laboratory. Thus we have guinea-pig (biologic) tests for tuberculosis, for the standardisation of various toxins and antitoxins, for determining immunity ; for estimating and standardising the activity of adrenalin, pituitrin, secretin ; for standardising anesthetics and narcotics. Experimental biology, experimental pharmacology, experimental physiology are based on biologic tests. In addition to these specially formulated biologic tests, the human organism in its response to environmental conditions constantly presents evidence of its infinite specific adaptations to physical and chemical energy. The specificity of the receptive mechanisms for light, for sound, for odours, for flavours ; the specific variations of the sense of touch ; the specific response of the respiratory centre to changes in the H-ion concentration of the blood ; the specific action of the hormones, such as adrenalin—the accuracy and specificity of action of these mechanisms far exceed the accuracy of our artificial and clumsy laboratory substitutes. These biologic tests are as accurate for man as for the dog and guinea-pig, but the clinician is more familiar with the behaviour of men than he is with the behaviour of laboratory animals. Deductions from the data of the laboratory serve to point the way to the ultimate interpretation which must be determined by more secure deductions from the data of the clinic. In our researches, therefore, as far as possible, we have tested the validity of our hypotheses and laboratory data by their application in the clinic.

As the evidence has accumulated, it has become increasingly difficult to maintain a neutral position. Realising the danger of this attitude of mind, we have repeated our experiments again and again with different observers ; we have secured as much objective evidence as possible—photomicrographs, blood-pressure tracings, etc. ; we have made many negative experiments ; we have sought diverse sources of evidence ; the findings of the laboratory worker have been tested in the clinic by other workers so that diversity of judgment might be assured ; and finally—and of greatest value—our earlier summaries and deductions have been published in various forms for the purpose of eliciting criticism—adverse criticism in particular. The criticisms have been many and varied and of inestimable value, for in many instances they have suggested new lines of investigation and they have tended always to speed the research.

Since our later researches have evolved from the work which has been reported in detail in the previous monographs, in order to present more fully

the criteria upon which we have constructed our hypotheses, we shall first give summaries of the earlier publications, following these with data of our more recent researches, and shall discuss some of the theories proposed for the explanation of shock and exhaustion. We shall consider the mechanism involved in shock, exhaustion, and restoration, and shall state the principles in accordance with which shockless operations may be performed. We shall attempt to apply physical laws in a consideration of the mechanism which transforms potential energy into kinetic energy; and shall offer a physico-chemical interpretation of certain normal and disease processes.

CHAPTER I

PHENOMENA OF EXHAUSTION

EXPERIMENTAL DATA

I. Exhaustion and Shock-Producing Effects of Traumatism and of Certain Drugs as Evidenced by Circulatory and Respiratory Changes

The following summaries of experimental findings reported in previous monographs (see p. 3) suggest that shock obeys the laws of physics, and that the degree of shock is proportional to the intensity and number of injurious contacts multiplied by the excitability of the injured tissue; thus these summaries provide the surgeon with a basis from which to estimate the shock-producing value of different types of operation upon the various organs and tissues, and reveal the basis of the shockless operation.

EFFECT OF TRAUMA OF VARIOUS TISSUES AND ORGANS UNDER ETHER ANESTHESIA

Effects of Trauma of Tissues

Skin.—Cutting and tearing the skin as a rule caused a rise in blood-pressure; in the exceptional cases, there was either no effect on the blood-pressure or a fall (Fig. 1). Late in the experiment, when the animal was exhausted, the rise in blood-pressure appeared less promptly. Burning the skin in every instance caused a marked rise in the blood-pressure (Fig. 2).

Traumatising the skin usually accelerated the respiration; burning the skin caused a greater acceleration of the respiration, sometimes a hyperpnea.

Injury of the skin of the paws caused much greater circulatory and respiratory changes than like injury of the skin in other regions. Our observations indicate that *the richer the nerve supply in a region, the more will injury of that region contribute to the production of shock.*

Connective Tissue.—Mechanical or thermal injury of connective tissue—fascia, tendons, ligaments, etc.—produced no appreciable effect.

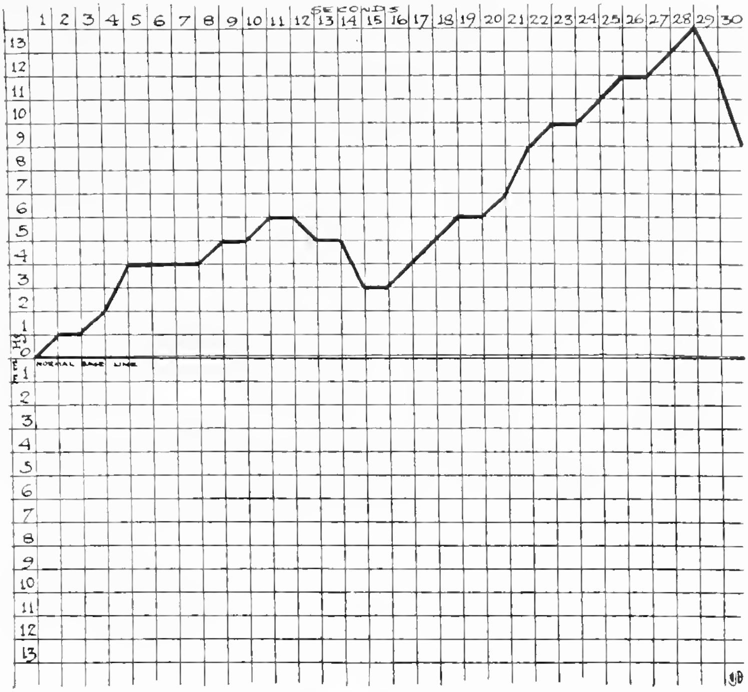


FIG. 1.—Effect on the Blood-Pressure of Cutting and Crushing the Skin. (Average of 22 Experiments.)

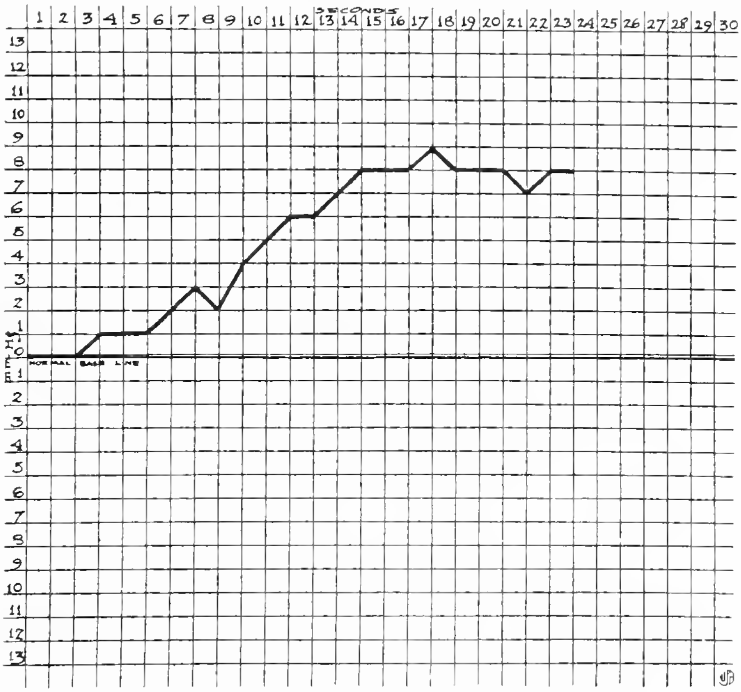


FIG. 2.—Effect on the Blood-Pressure of Burning the Skin. (Average of 58 Experiments.)

Muscles.—The cutting or crushing of muscles caused changes in the respiration and in the circulation less marked than those which result from injuries of the skin ; in many experiments the blood-pressure fell.

Bones.—In some instances the rough separation of the periosteum from the bone caused effects similar to those produced by the trauma of skin and muscle. In other cases, no such effect was produced. Sawing through bones, whose periosteum had not been previously removed, sometimes was attended

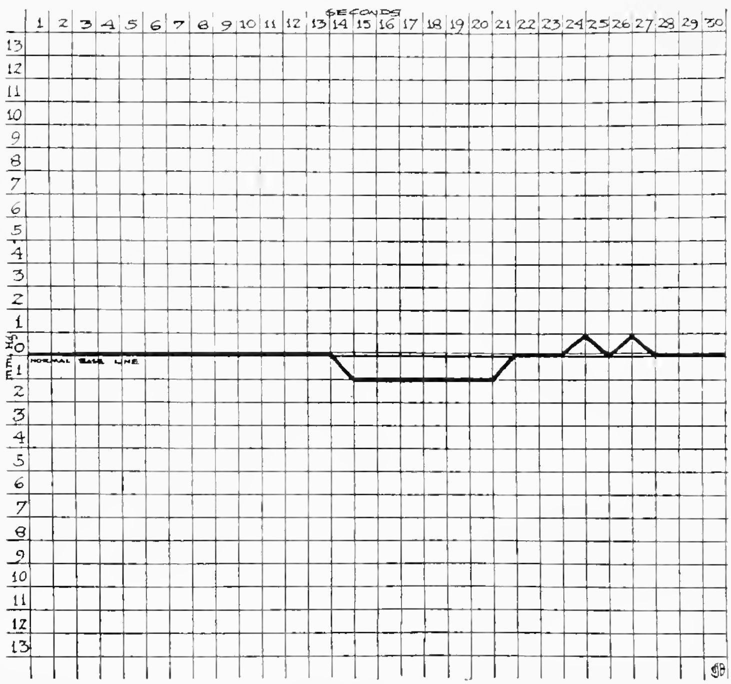


FIG. 3.—Effect on the Blood-Pressure of Crushing and Sawing Bone. (Average of 20 Experiments.)

by a slight rise in blood-pressure and corresponding respiratory changes (Fig. 3). But sawing, cutting, crushing, and breaking bones, whose periosteum had previously been removed, was not, in any instance, attended by any alteration in either the blood-pressure or the respiration. This was true also of injuries to cartilage.

Joints.—Cutting, sawing, curetting, or crushing the joints, *per se* produced no appreciable effect (Fig. 4).

Nerve-Trunks.—When nerve-trunks were stretched, crushed, torn, contused, or cut with dull instruments there usually resulted a rise in blood-pressure

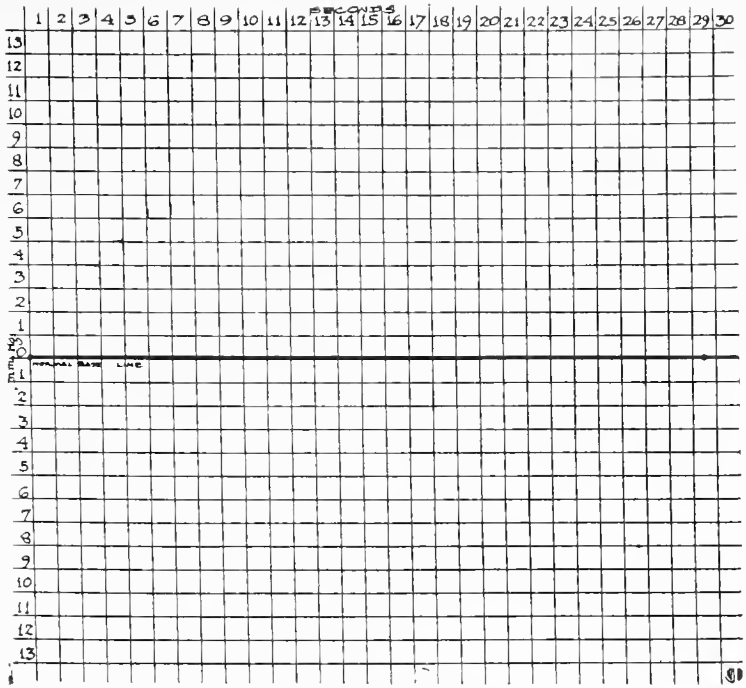


Fig. 4.—Effect on the Blood-Pressure of Opening and Operating on Joints. (Average of 10 Experiments.)

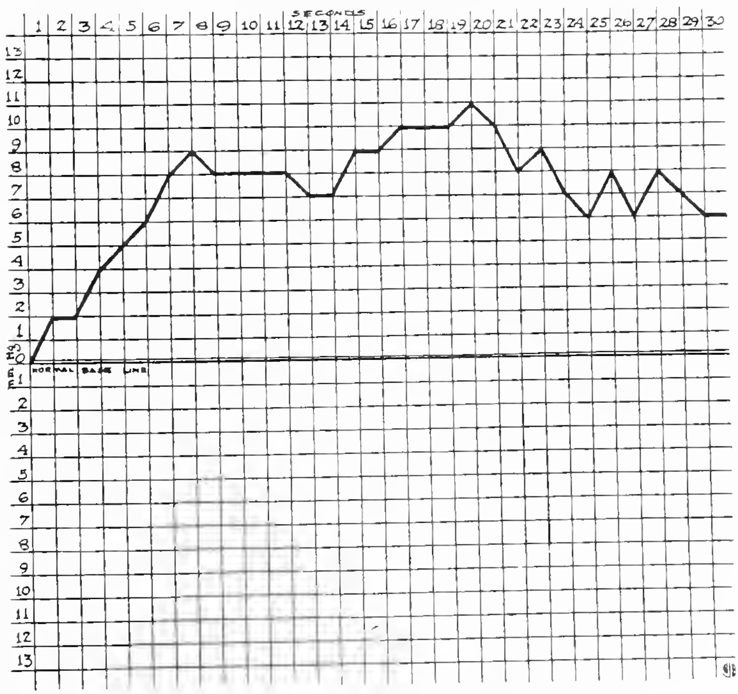


Fig. 5.—Effect on the Blood-Pressure of Stretching Nerve-Trunks. (Average of 29 Experiments.)

followed by a fall occasionally to the normal level, but more often lower (Fig. 5); sometimes it fell far below the normal level. Vaso-motor disturbances frequently became more prominent immediately after the injury of nerve-fibres, indicating disturbed metabolism of the vaso-motor centres. When the nerves were repeatedly injured, the mean blood-pressure, which fell somewhat after each experiment, suffered further depressions in proportion to the intensity and duration of each irritation. In some instances, especially after repeated

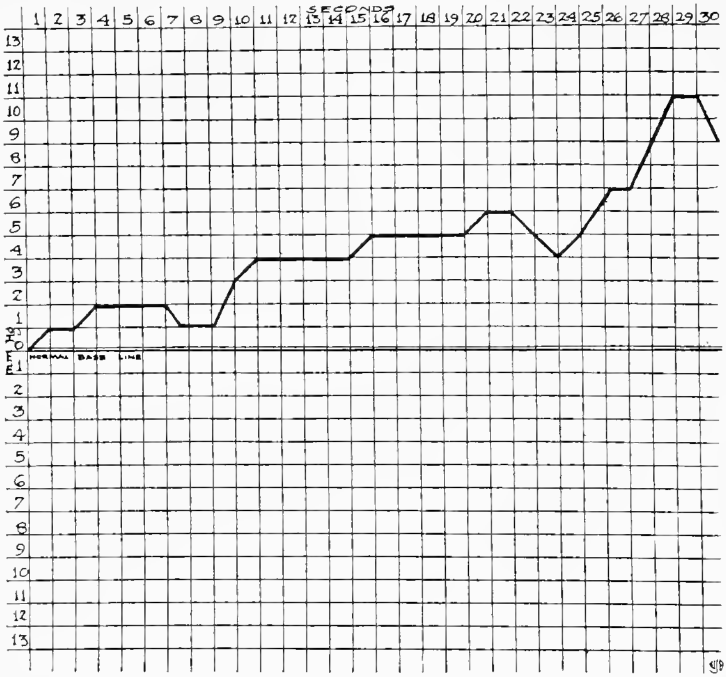


Fig. 6.—Effect on the Blood-Pressure of Crushing and Cutting the Turbinated Bones, and Forcibly Dilating the Nares. (Average of 10 Experiments.)

injury, the blood-pressure did not rise, but fell immediately, the decline being usually quite gradual and continuous. Severing the nerves quickly with sharp scissors usually affected the blood-pressure comparatively little; if it rose, the rise was but momentary; if it fell, the decline was immediate and usually without later return to normal. The total disturbance of the blood-pressure was decidedly less when the nerves were quickly severed with a sharp instrument, than when they were dragged upon, contused, torn, etc. Electric or thermal irritation of nerves caused blood-pressure changes very similar to, though more marked than, those caused by mechanical irritation.

In every instance the total respiratory volume was much increased. *But after the animal had become very weak, or after repeated irritation of a given nerve-trunk, there was sometimes a fall in the blood-pressure without any preliminary rise.*

Effect of Trauma of Regions and Organs

Head.—Various forms of mechanical injury of the *nares,* including contusion, laceration, dilatation, and crushing of the turbinated bones, each caused

Fig. 7.—Effect on the Blood-Pressure of Severe Manipulation of the Posterior Nares. (Average of 10 Experiments.)

a distinct rise in blood-pressure (Fig. 6). The respiratory rate was diminished. Imitation of the forcible removal of a tumor from the posterior nares in some instances caused a partial inhibition of the respiration and of the heart (Fig. 7).

Injury of the *eye* caused no notable change in the blood-pressure or the respiration (Fig. 8).

Injury of the *tongue* slightly affected the blood-pressure and the respiration, but forcibly dragging the tongue out of the mouth caused partial inhibition

of the respiration and of the heart. *This observation carries a warning to anesthetists.*

Even slight contacts with the under surface of the *pharynx* near the base of the epiglottis and the superior opening inhibited the respiration. More vigorous manipulation produced cardio-inhibitory effects also. Manipulating the interior of the larynx caused a striking inhibition of both the respiration and the circulation (Fig. 9). A preliminary hypodermic injection of atropin

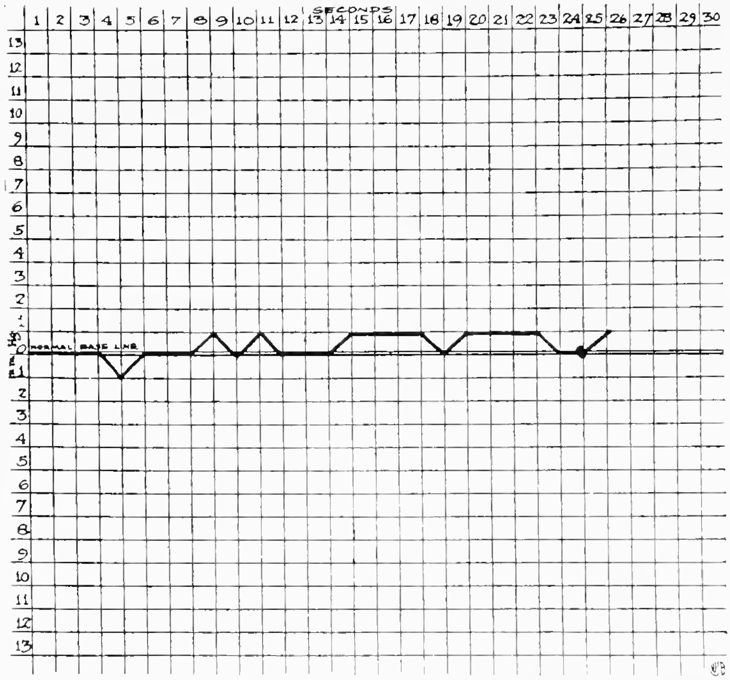


FIG. 8.—Effect on the Blood-Pressure of Injury and Enucleation of the Eye. (Average of 10 Experiments.)

prevented the cardiac inhibition; while the local application of cocain protected both the respiration and the circulation against any effect of laryngeal irritation (Figs. 10 and 11). Like protection was secured by division of the superior laryngeal nerves.

Brain.—Gentle separation of the dura mater from the skull caused but little if any disturbance of the respiration or the circulation.

No amount of trauma—not even the gradual destruction and piecemeal removal of the hemispheres caused any changes in the blood-pressure or the respiration, provided that no pressure effects were transmitted to the base of

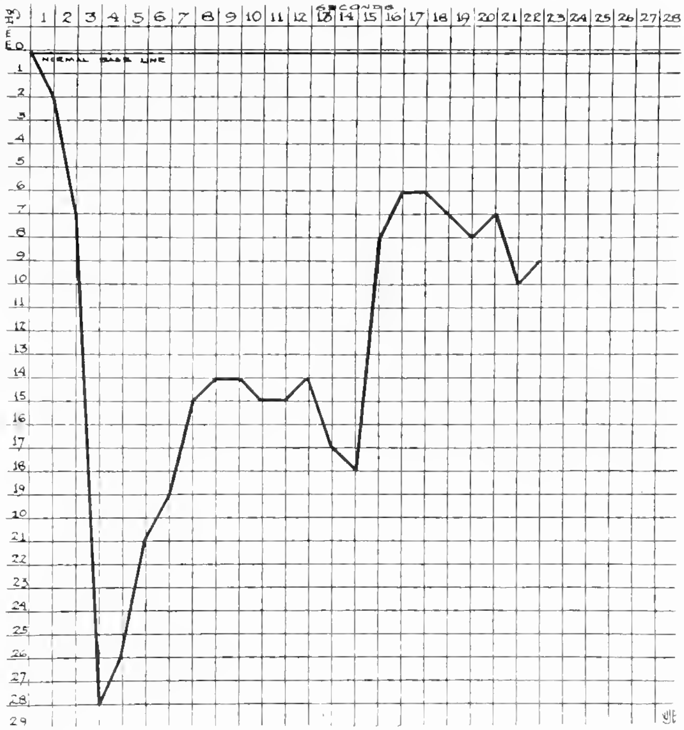


Fig. 9.—Effect on the Blood-Pressure of Manipulation of the Larynx. (Average of 10 Experiments.)

Fig. 10.—Effect on the Blood-Pressure—*A*, of Manipulation of the Larynx; *B*, of Manipulation of the Larynx after the Use of Cocain. (Average of 10 Experiments.)

the brain and that there was little or no hemorrhage. Increased intracranial pressure caused the blood-pressure to rise.

Gunshot wounds of the hemispheres in most instances caused enormous sweeping 'vagal' heart-beats—though sometimes the circulation was ac-

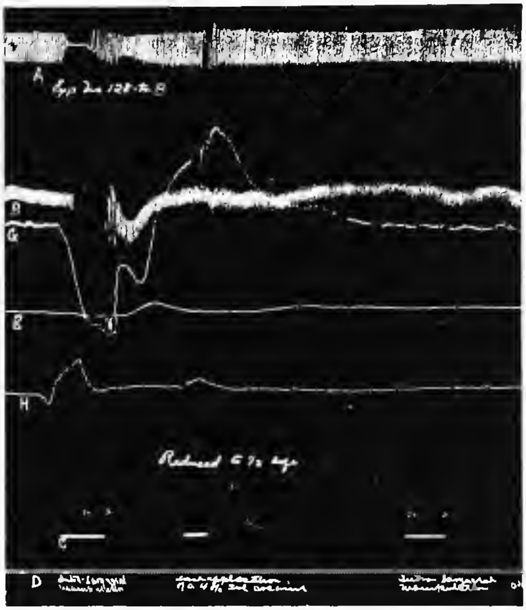


FIG. 11.—Effect on the Blood-Pressure and Respiration of Intra-Laryngeal Manipulation Before and After the Local Application of Cocain.

A, respiration; *B*, central blood-pressure; *G*, portal pressure; *H*, heart; *C*, signals. Note the complete arrest of respiration during intra-laryngeal manipulation as shown above the first signal on the left. The middle signal marks the local application of a four per cent. solution of muriate of cocain upon the laryngeal mucosa. Note slight inhibition of heart and temporary arrest of the respiration. Signal at the right marks the application of severe intra-laryngeal manipulation and the application of cocain as above. Note the absence of changes in the tracing.

celerated, while the respiration was instantly and in some cases permanently arrested. Injury of the medulla caused a momentary rise of the blood-pressure followed by a staggering fall to zero (Fig. 12).

Neck.—Excluding contact with the vagi or with the sympathetic nerves, trauma of the deep tissues of the neck caused little disturbance of the circulation or respiration.

Thorax.—Injuries of the thoracic region—resection of the ribs, stab wounds, gunshot wounds, etc., in experiments in which the thoracic cavity was not opened, produced only the effect of such injuries upon the tissues involved—skin, muscle, or bone. Opening the thorax was attended by grave irregularity of the rate and rhythm of the respiration; the blood-pressure underwent sweeping changes; and the pulse-wave usually became short and irregular

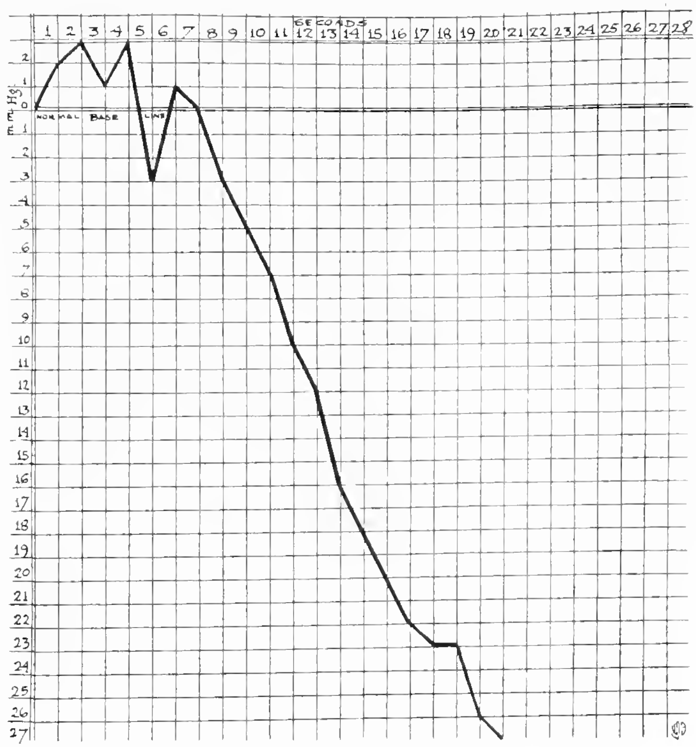


FIG. 12.—Effect on the Blood-Pressure of Crushing the Medulla. (Average of 10 Experiments.)

(Fig. 13). In no other experiments were such exceedingly irregular effects on the blood-pressure and respiration produced as in intra-thoracic procedures. The pulse and respiration quickly improved after the chest had been closed air-tight.

Field surgery in this war has amply confirmed these experimental observations. Air-tight closure in particular has proved to be of value in the treatment of chest wounds.

Heart.—The slightest direct contact with the heart caused marked changes

(Fig. 14). Incising the pericardium produced but little effect. Puncturing the heart with a scalpel caused only the lapse of from one to several beats. A gunshot wound of the heart, which did not penetrate the chambers, caused only temporary arrhythmia.

Lungs.—Mechanical injury of the lungs produced by manipulation, contusion, stabbing, gunshot wounds, etc., on the whole seemed to have a greater effect

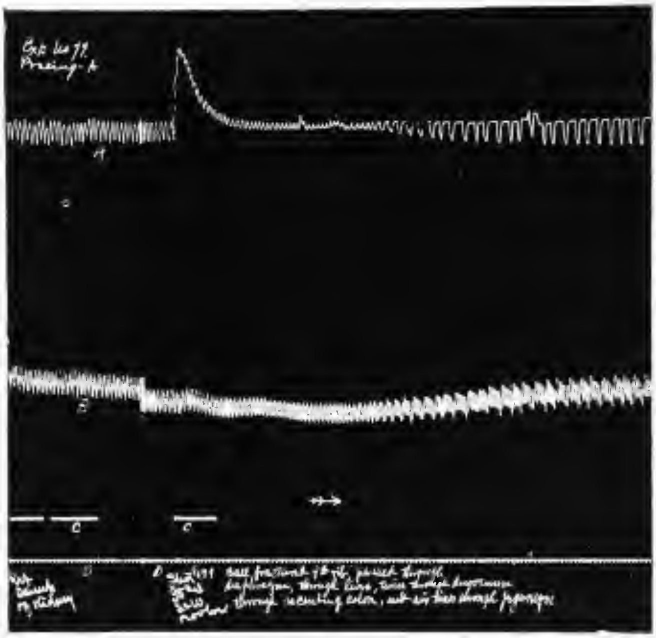


Fig. 13.—Effect on the Blood-Pressure and Respiration of a Gunshot Wound of the Chest.

A, respiration; *B*, central pressure; *C*, signals; *D*, seconds. At the third signal-mark the animal was shot. The ball fractured the ninth rib, passed through the diaphragm, through the liver, twice through the duodenum, through the ascending colon, and six times through the jejunum.

upon the heart than upon the respiration, but it was very difficult to determine this point. In some cases very marked 'vagal' heart-beats resulted from pinching the lungs with the fingers. The application of this observation in the operating theatre by the use of gentle and precise manipulations has proved of great advantage.

Large Blood-Vessels.—Injury of the venous trunks caused marked changes in blood-pressure as a result of the mechanical interference with the flow of blood into the chambers of the heart. In fresh animals the lost equilibrium

was promptly restored, but this was not the case when the animals were exhausted before the cardiac equilibrium was disturbed.

Diaphragm.—Every contact, however slight, with the abdominal side of the diaphragm caused markedly arrhythmic respiration. When the contact was extensive, every part of the respiratory curve became irregular.

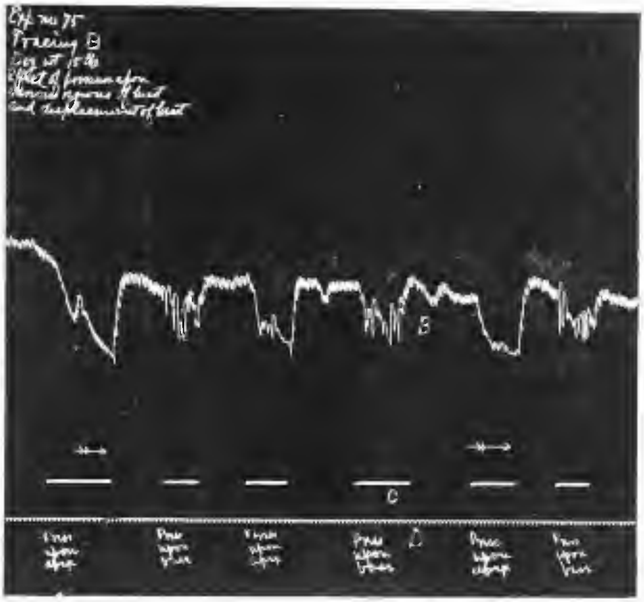


FIG. 14.—Effect on the Blood-Pressure of Contact with the Heart.

The tracing in the centre of the cut represents the central blood-pressure. The striking irregularities are due to contact with different portions of the heart as indicated on the cut. Note the sudden drop in blood-pressure on contact followed by a rapid rise on its cessation. Note also the longer strokes caused by contact with the base as compared with the effect of contact with the apex.

Puncture of the diaphragm and gunshot wounds usually caused the immediate arrest of the respiration—sometimes permanent, or if temporary, there was a tendency to respiratory failure later in the experiment.

The mere exposure of the chest to the air was shown to be progressively injurious. This fact raises the interesting query :—With the action of what mechanism has mere exposure of the chest interfered and how has that interference reduced the vitality ?

Abdomen—Peritoneum.—Incision of the peritoneum produced a fall in blood-pressure, but this was not always immediate (Figs. 15-17). When the abdominal contents *in situ* were exposed to the air, the blood-pressure fell

gradually. Every contact, however slight, with either the parietal or the visceral peritoneum caused markedly arrhythmic respiratory action and a fall of blood-pressure (Fig. 18). Manipulation of the diaphragmatic peritoneum produced most marked respiratory changes; and tolerance was not secured

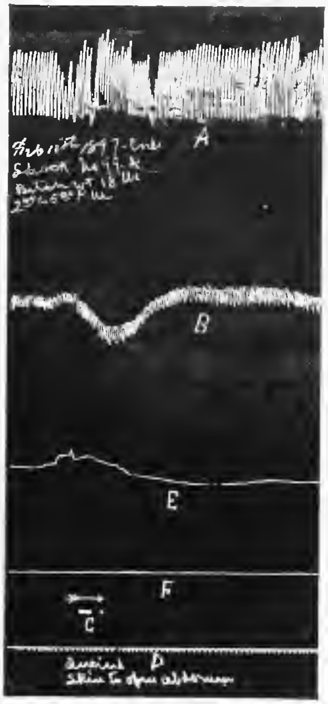


Fig. 15.—Effect on the Blood-Pressure and Respiration of Incising the Skin in Making an Abdominal Section.

A, respiration; *B*, central blood-pressure; *E*, peripheral venous pressure in femoral. Note the fall in the central pressure after a temporary rise, and the rise in the peripheral venous pressure.

Fig. 16.—Effect on the Blood-Pressure and Respiration of Incising the Skin of the Abdomen.

Upper tracing represents respiration, the middle the central blood-pressure. Note the respiratory change and the decline in the blood-pressure.

by continuing the manipulations unless they were confined to the same area. We secured abundant proof that continued peritoneal excitation exhausts the respiratory mechanism.

Manipulation of the peritoneum and its mere exposure caused rapid dilatation of the vessels of the mesentery and of the hollow viscera. The viscera became red at first, and gradually livid after further exposure. The rapidity with

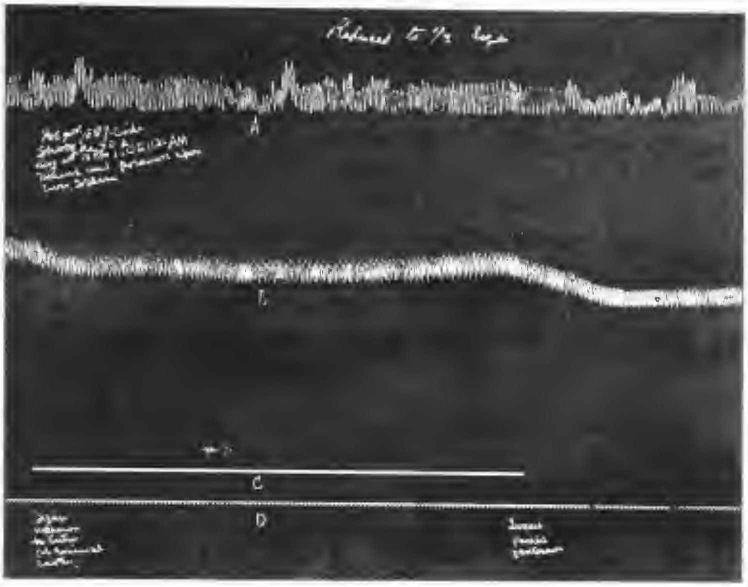


Fig. 17.—Effect on the Blood-Pressure and Respiration of Cutting Through the Abdominal Wall and Opening the Peritoneal Cavity.

A, respiration; *B*, central blood-pressure; *C*, cutting through the abdominal wall. Note the fall on cutting the skin and on opening the abdominal cavity, also the respiratory alterations. The peritoneum was incised at the end of the signal, and during the time marked by the signal the abdominal wall was being incised.

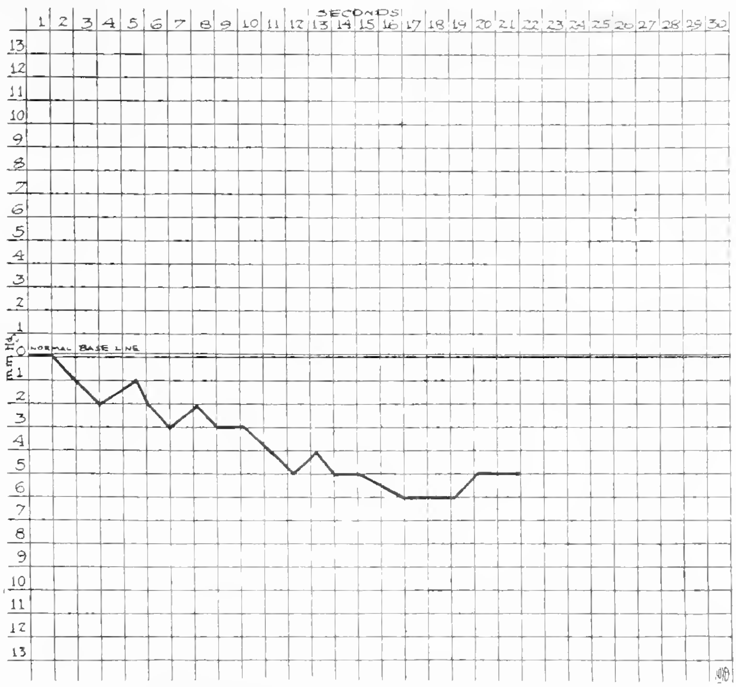


Fig. 18.—Effect on the Blood-Pressure of Manipulation of the Parietal Peritoneum. (Average of 10 Experiments.)

which the lividity developed bore some relation to the respiratory as well as to the circulatory disturbance. The mesenteric veins became more prominent, especially the small venous radicles at the base of the intestines. With long exposure and great irritation even the transparent peritoneal spaces in the mesentery displayed vessels and sometimes became red. The arteries at first seemed larger and pulsated more distinctly: but later, when the blood-pressure had become quite low and the intestines livid, scarcely any pulsation was visible.

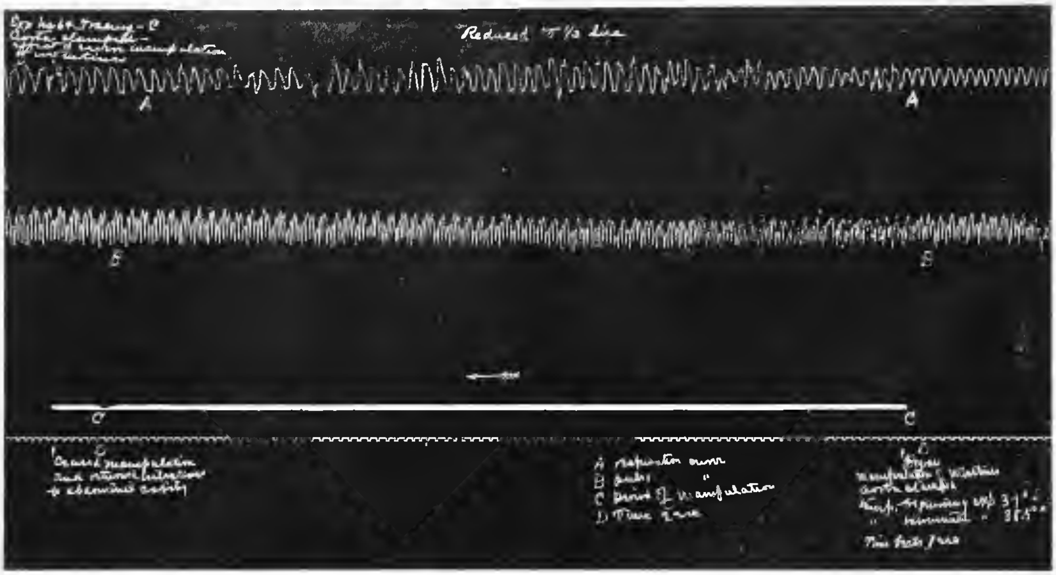


FIG. 19.—Effect on the Blood-Pressure and Respiration of Manipulation of the Intestines after the Intra-thoracic Clamping of the Aorta.

A, respiration; *B*, blood-pressure; *C*, signal; *D*, seconds. Aorta clamped within the chest; severe manipulation of the intestines produced no effect upon the blood-pressure, but the respiration curve was irregular.

With the development of these vascular changes the blood-pressure fell. The more severe the injury, the greater the extent of contact and exposure, the more rapid was the decline of the blood-pressure. On the other hand, in exceptional cases extensive and continued manipulation for as long as twenty minutes, and in one case for half an hour, scarcely altered the blood-pressure. In weak animals, or late in an experiment, the rate of decline of the blood-pressure was increased. A water manometer in the splenic vein, with its cannula pointing toward the heart, showed a decided rise in a number of observations during the development of shock from abdominal exposure and

injury. While the central blood-pressure was declining the portal pressure was rising, showing an increase of blood in the latter area.

In one series of experiments in which the arterial supply of the splanchnic area was clamped subperitoneally, before and during trauma, shock was delayed but not prevented (Fig. 19). Clamping the superior mesentery alone diminished but did not prevent the usual rapidity of the development of splanchnic shock.

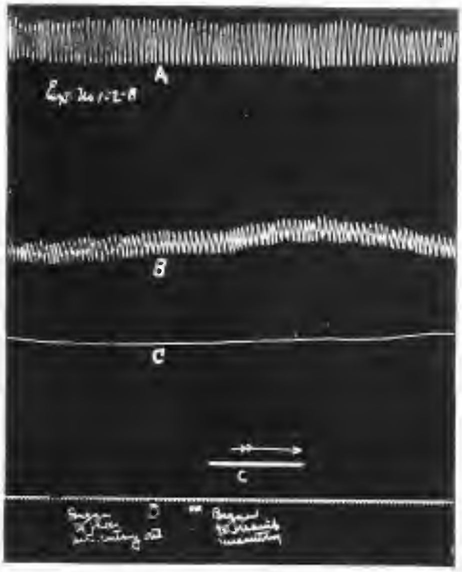


FIG. 20.—Effect on the Blood-Pressure and Respiration of Manipulation of the Omentum.

A, respiration; *B*, central blood-pressure; *C*, signal; *D*, time in seconds. Note the slight rise in blood-pressure and the lack of any effect upon the respiration in contrast to the fall of blood-pressure on manipulating the intestines. (Note: An error in the cut—substitute *omentum* for *mesentery*.)

The results of manipulation of the omentum were antithetic to those produced by manipulation of the peritoneum (Fig. 20).

These observations lead to the following practical applications in abdominal surgery:—(*a*) Surgical operations on the abdomen should be as brief as is consistent with good work; (*b*) manipulations should be as light and as few as possible; (*c*) exposure should be as slight in extent and as brief as is consistent with the demands of the operation.

Liver.—Manipulation of the liver caused no effect beyond that due to

hemorrhage and to the unavoidable manipulation of its covering peritoneum. The interior of the liver is as negative in its response to injury as are the protected brain and the protected deep planes of tissue in the back and in the neck. This important fact may perhaps be explained by the phylogenetic importance of the liver.

Adrenals.—Manipulation of the adrenals caused a rise in the blood-pressure,

Fig. 21.—Effect on the Blood-Pressure of Manipulation of the Adrenal Glands. (Average of 10 Experiments.)

which may have been due to the mechanical forcing of adrenalin into the circulation (Fig. 21).

Spleen.—Excepting the response due to injury of its covering peritoneum, no special results of manipulation of the spleen were noted.

Urinary Bladder.—Cutting, compressing, over-distending, or otherwise injuring the bladder caused a rise in blood-pressure in a few instances, but in many of the experiments no effect was noted.

Uterus.—Incision, contusion, manipulation or any other mechanical injury of the uterus in every instance caused the blood-pressure to rise. The rise appeared rather slowly, but in many instances was marked. Sometimes

the blood-pressure gradually declined to its former level, but, for some time at least, it tended to remain at the level to which it had risen (Fig. 22).

Male Genital Organs.—Injury of the testicles, of the spermatic cord, of the tunica vaginalis or even of the skin of the scrotum in most instances caused a fall in the central blood-pressure, the fall appearing after a brief interval (Fig. 23). While the central pressure was falling the portal pressure was usually rising as markedly. This observation suggests that splanchnic dilatation was

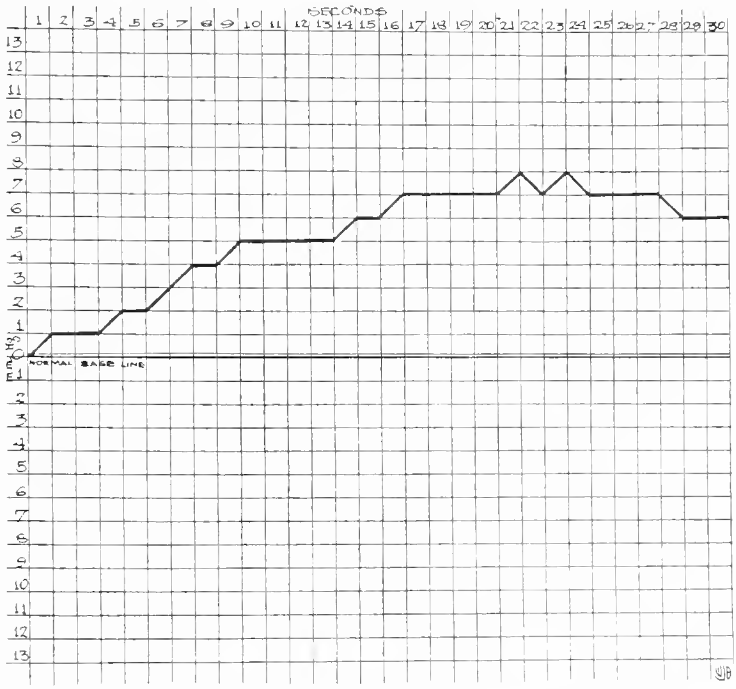


FIG. 22.—Effect on the Blood-Pressure of Manipulation of the Uterus. (Average of 14 Experiments.)

the cause of the fall in the central pressure. The blood-pressure usually returned to its former level. The injection of cocain into the testicle, into the tunica vaginalis, or into the spermatic cord, prevented the fall in the central blood-pressure and the rise in portal pressure; it also prevented respiratory alterations (Fig. 24, compare with Fig. 23).

Rectum and Anus.—Forcible dilatation of the rectum and of the anus caused usually a rise, but sometimes a fall, in the blood-pressure and an increase in the frequency and depth of the respiration (Figs. 25 and 26). These changes were prevented by preliminary infiltration of the anal area with a local anesthetic.

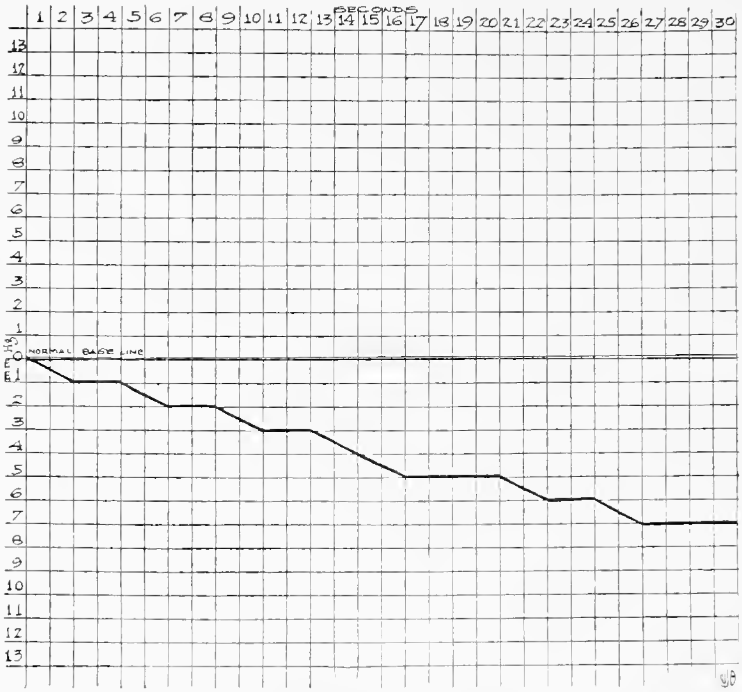


FIG. 23.—Effect on the Blood-Pressure of Manipulating and Crushing the Testicle. Many of the Experiments Exhibited a Sudden and Profound Fall, not Represented in the Average. (Average of 41 Experiments.)

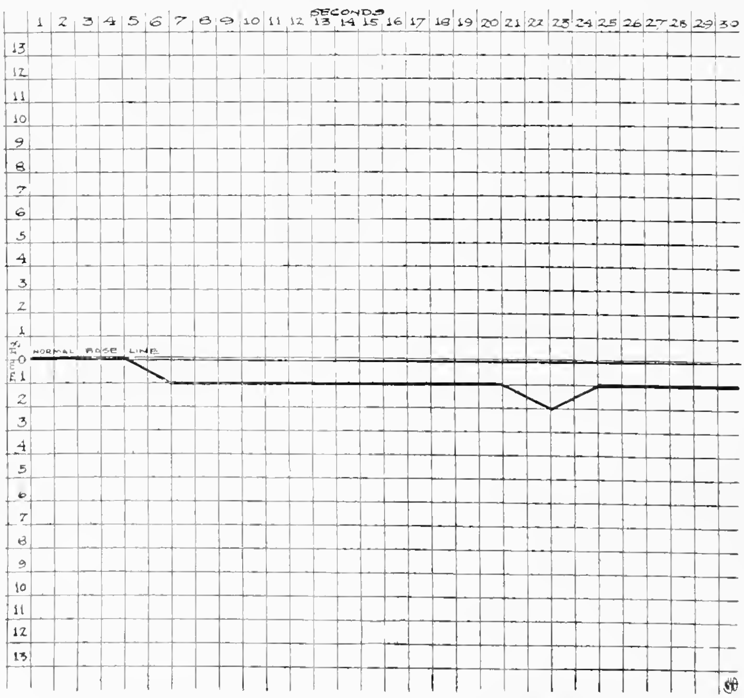


FIG. 24.—Effect on the Blood-Pressure of Crushing the Testicle after Injecting Cocain into the Cord. (Average of 10 Experiments.)

Extremities.—Injury of the extremities—cutting, crushing, fracturing, burning, or amputating (without loss of blood)—was usually attended by a preliminary rise in blood-pressure, followed by a fall to a lower level than before the injury (Fig. 27). The respiration was much altered in rhythm and was temporarily increased in frequency. Traction on the nerve-trunks, in particular, markedly affected both the respiration and the circulation. *The resultant shock in these experiments made without the loss of blood was in direct*

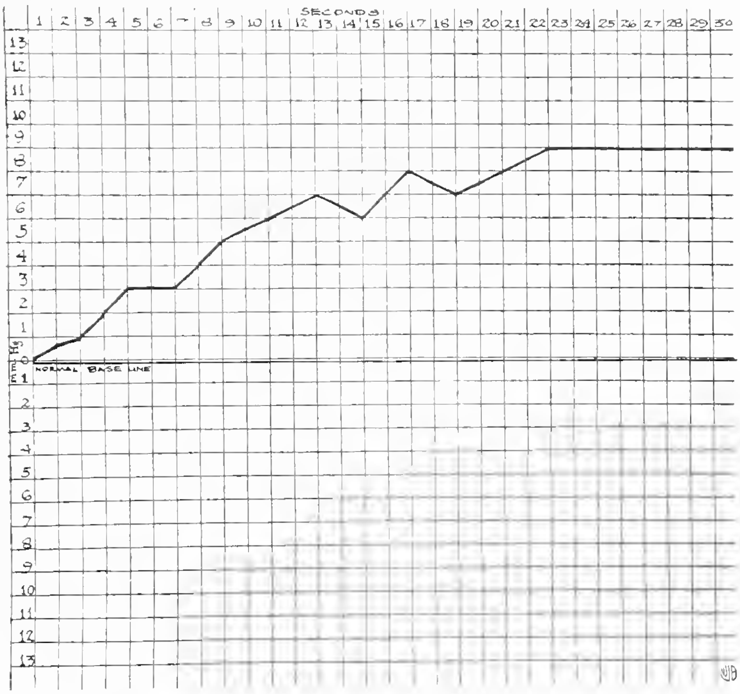


FIG. 25.—Effect on the Blood-Pressure of Forcible Dilatation of the Anus. (Average of 11 Experiments.)

proportion to the amount of excitable tissue injured and to the protraction of the manipulation. Injury of the paws was more productive of shock than injury of any other superficial part of the extremities. These experiments supply sufficient evidence that the shock produced by injury is in direct proportion to the nerve supply of the part injured.

In contrast to the above observations is the fact that no amount of burning, cutting, or crushing caused any notable change in the circulation or the respiration provided the central nervous system had been previously disconnected from the injured area by the blocking of the nerve supply with a local anesthetic

(Fig. 28). This fact supplied the fundamental principle of the shockless operation.

EFFECT OF CERTAIN DRUGS

Strychnin and Adrenalin

Strychnin causes a higher rise in blood-pressure than any other drug except adrenalin (Fig. 29). Either strychnin or adrenalin may double the

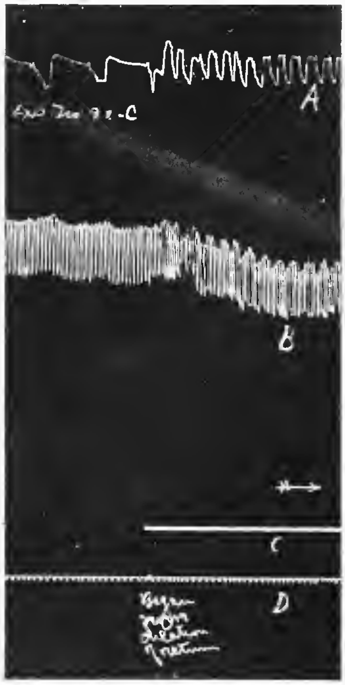


Fig. 26.—Effect on the Blood-Pressure and Respiration of Dilatation of the Rectum.

A, respiratory curve; *B*, blood-pressure curve. The effect upon the blood-pressure was but temporary.

blood-pressure, but these two drugs owe their great blood-pressure raising power to opposite intermediate effects:—strychnin stimulates the central vaso-motor mechanism; adrenalin stimulates the musculature of the heart and the blood-vessels.

This being the case, then, if the vaso-motor mechanism is exhausted in

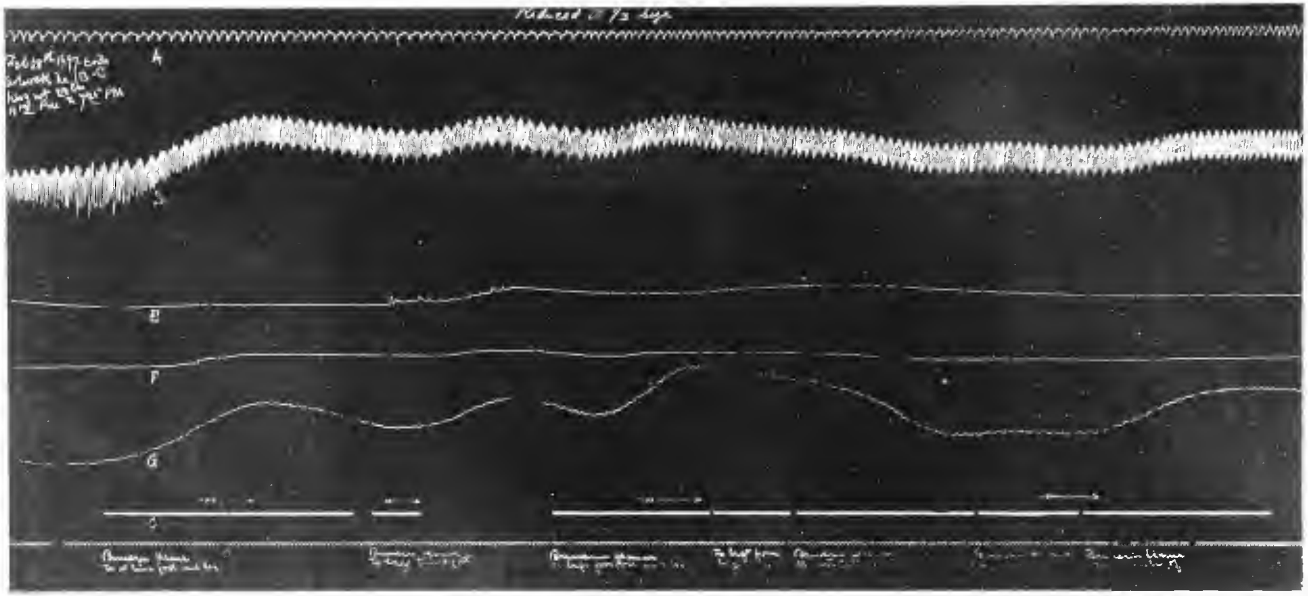


FIG. 27.—Effect on the Blood-Pressure and Respiration of Burning the Extremities.

A, respiration; B, central blood-pressure; C, signal; D, seconds; E, peripheral venous pressure in femoral; G, portal pressure. Characteristic results of injury of tissues of the extremities. Note the rise in all the pressures. The respiratory apparatus did not register satisfactorily, owing to disarrangement in the first part of the experiment.

shock, the effect of strychnin would progressively diminish as the degree of shock increases. On the other hand, if the muscles of the blood-vessels are normal in shock, and the vaso-motor centres are exhausted, adrenalin would still cause a large rise in blood-pressure.

The following are the results of our experiments to determine this point :—

In curarised but otherwise normal animals, and in animals in which both vagi and both accelerantes had been severed, the rise following a physiologic

FIG. 28.—Effect on the Blood-Pressure—*A*, of Burning Foot as Control Experiment; *B*, of Burning Opposite Foot after Injecting Cocain in the Sciatic and Anterior Crural Nerves. (Average of 10 Experiments.)

dose of strychnin continued for from one-half to one and a half hours. After a second equal dose the blood-pressure rose in a few instances as high as after the first dose, but usually not as high, and on the average was not maintained more than half as long. After a third equal dose the blood-pressure generally rose, but not as high as after the first two doses and was maintained for a much shorter period, usually but a few minutes. With later repetitions of the dose a period was soon reached when no further effect was noted (Figs. 30-32).

After each dose, when the effect of the drug had worn off, the blood-pressure fell to a point below its level before the dose was given, until finally it reached a level, usually between twenty and thirty mm., which was not altered by further dosage. If *during* the time of maximum rise following a physiologic dose an equal or greater dose was given, there followed an additional temporary rise of from five to ten mm., which was maintained but a few seconds.

During the period in which repeated doses of strychnin continued to cause the blood-pressure to rise, burning the paw or electrical stimulation of the sciatic nerve was followed by a rise in blood-pressure to about the same height but of less duration than in the normal animal.

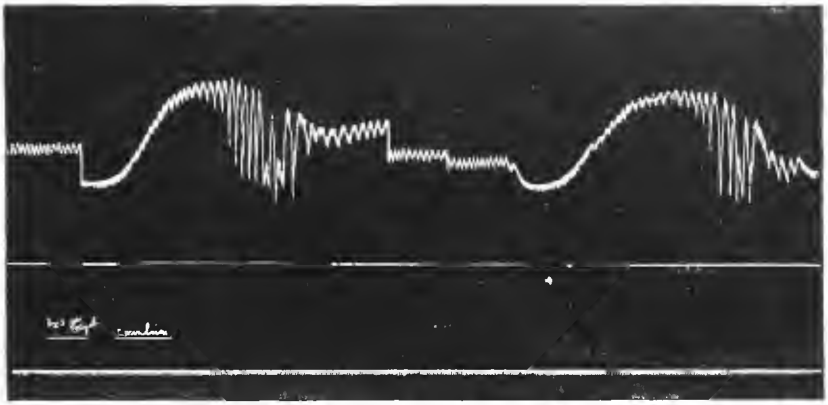


FIG. 29.—Effect on the Blood-Pressure of the Injection of Strychnin.

Note the marked rise in the blood-pressure following the injection of 1/20 grain of strychnin. The long excursions were caused by the convulsions. After the animal became quiet peripheral stimulation caused a second convulsion.

On the other hand, *when strychnin no longer caused the blood-pressure to rise, no rise was produced by burning the paw or electrically stimulating the sciatic nerve.*

During the maximum stimulation, the blood-pressure curve was usually even, but as the strychnin effect diminished, the curve became irregular. Between the end of the maximum curve and the beginning of the final breakdown, the curve was quite irregular. After the inauguration of the final breakdown, the curve became still more irregular. When this stage was reached, it was not possible to distinguish between the terminal curve in the strychnin experiments and the terminal curve in the shock experiments.

After the blood-pressure had reached this terminal stage, the intravenous administration of saline solution caused a rise which continued for a limited time during the infusion; if the infusion was stopped, or if it

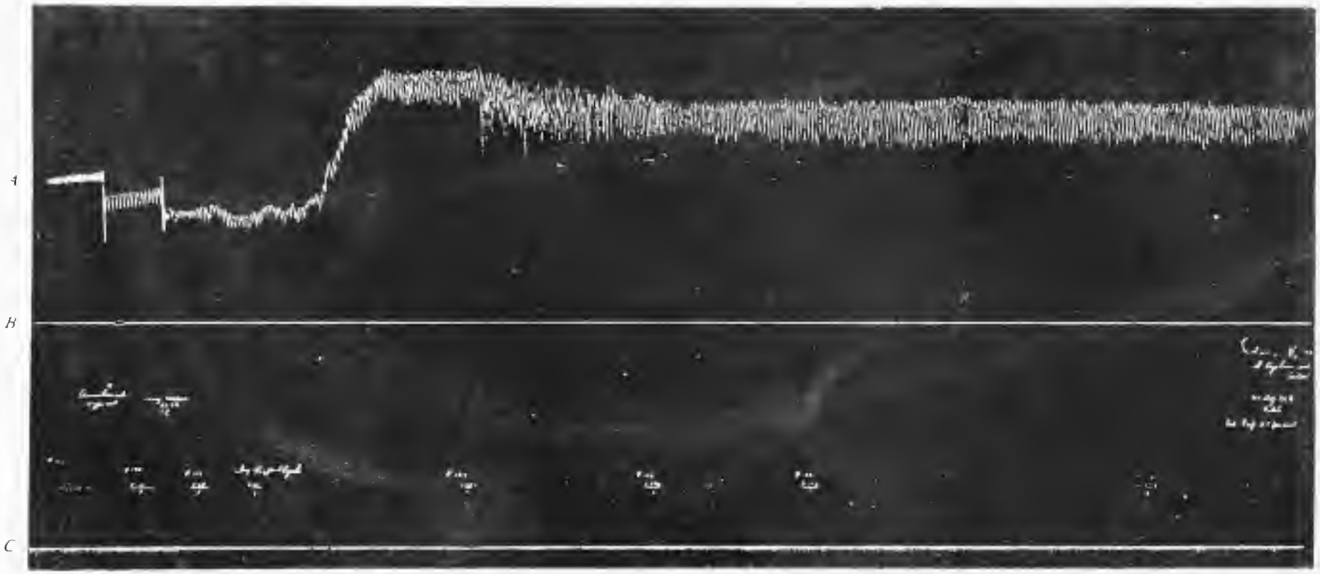


FIG. 30.—Effect on the Blood-Pressure of Repeated Doses of Strychnin. (I.) See also Figs. 31 and 32.

A, arterial blood-pressure; *B*, abscissa line; *C*, time in seconds. This tracing was obtained from a normal animal in which both vagi and both accelerantes had been severed and a physiologic dose of curare given. Two milligrammes of strychnin were given intravenously. Note the abrupt and sustained rise in the blood-pressure; also note the marked increase in the length of the pulse-waves. The two following cuts are continuations of this experiment. This experiment is intended to illustrate the exhaustion of the vaso-motor centre by the stimulating effects of strychnin.

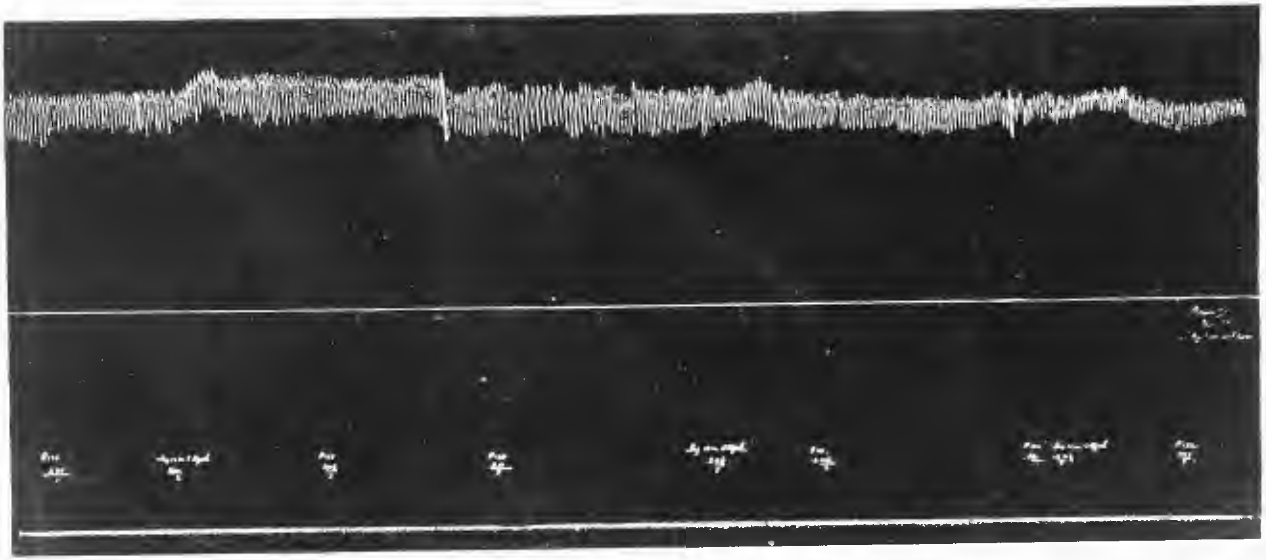


FIG. 31.—Effect on the Blood-Pressure of Repeated Doses of Strychnin. (2.) See also Figs. 30 and 32.

Note the continued high pressure, and the gradual decline in the length of the pulse-wave as compared with Fig. 30. Three additional doses of strychnin, of two milligrammes each, were given, none causing more than a slight momentary rise.

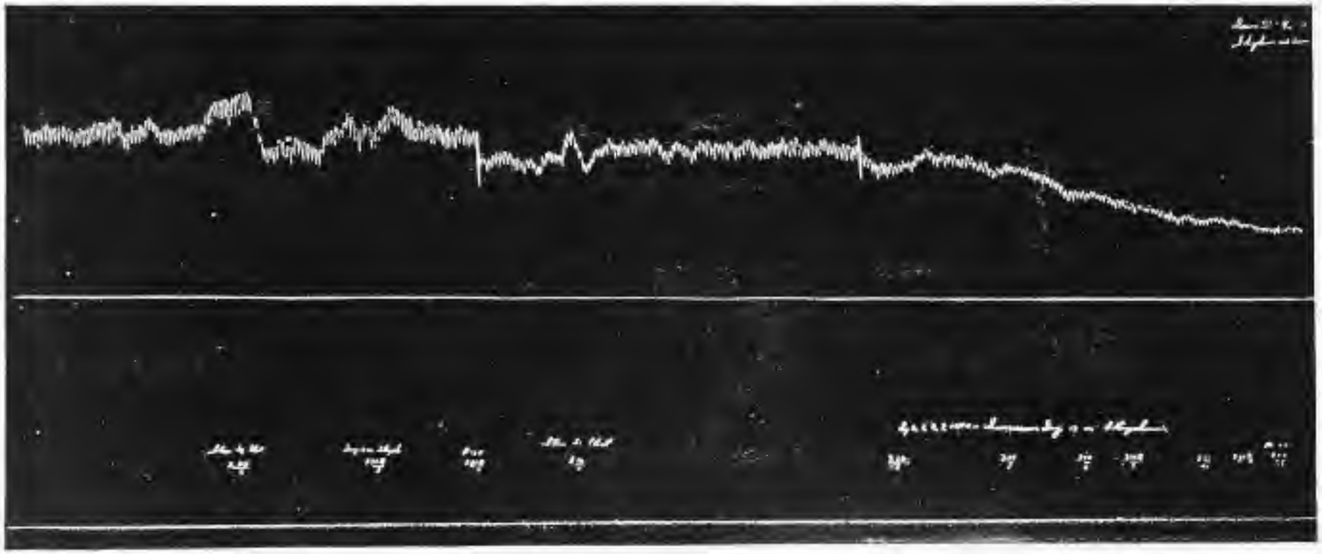


FIG. 32.—Effect on the Blood-Pressure of Repeated Doses of Strychnin. (3.) See also Figs. 30 and 31.

Note the markedly irregular blood-pressure curve, the diminution in the length of the pulse-wave, and the rapid decline in the blood-pressure. Repeated injections of strychnin caused no further change in the pressure. Stimulating the sciatic nerve and burning the paw no longer caused a rise in the blood-pressure, indicating the exhaustion of the vaso-motor centre.

was continued beyond a limited time, the blood-pressure fell to, or near, its former level.

The administration of adrenalin, after the final strychnin breakdown had occurred, was followed by a rise in proportion to the amount of adrenalin given—in one instance as high as 260 mm. Hg. Bandaging and other means of external pressure, if applied in the terminal stage, caused the blood-pressure to rise.

In the animals in which both vagi and both accelerantes had been severed, no change in the pulse-rate was noted. In animals in which varying degrees of shock had been produced, strychnin caused a rise in the blood-pressure inversely proportional to the degree of shock. In the cases in which but slight shock existed, the rise and its continuation were correspondingly great (Fig. 33). On repeating the injections, usually no rise occurred. In the cases in which shock was developed to nearly the fatal degree, only a slight rise occurred, lasting but a few minutes, after which no amount of strychnin produced a rise (Fig. 34). In any degree of shock, after the administration of a therapeutic dose of strychnin, the animals passed into deeper shock.

In the experiments in which the animals were bled until the blood-pressure had fallen to a level the same as that in the final breakdown from excessive doses of strychnin, the administration of therapeutic doses of strychnin caused a marked rise in the blood-pressure. In the experiments in which the *medulla was cocainised* and therapeutic doses of strychnin were given, causing convulsions, but a temporary slight rise in the blood-pressure occurred and only during the convulsions. In another series, in which both the medulla and the spinal cord were cocainised and an excessive dose of strychnin given, convulsions did not occur and no rise in blood-pressure was noted. In these experiments adrenalin caused a rise in the blood-pressure proportional to the dose—a rise as high as 260 mm. Hg.

These experiments show that sufficient traumatism alone, or sufficient strychnin alone, causes exhaustion of the vaso-motor centres ; that exhaustion of the vaso-motor centres may be produced in part by strychnin and in part by trauma, complete exhaustion of the vaso-motor centres being the result of their combined action.

Atropin

Atropin, hypodermically administered, was an efficient protection against cardiac inhibition in operations within the ' inhibition area ' in the larynx, and in such other operations as might cause mechanical stimulation of the vagi.

Local Anesthetics

Local Anesthesia applied to nerve-tissue entirely inhibits its function. Nerve-trunks may be physiologically ' blocked ' by a local anesthetic, so that

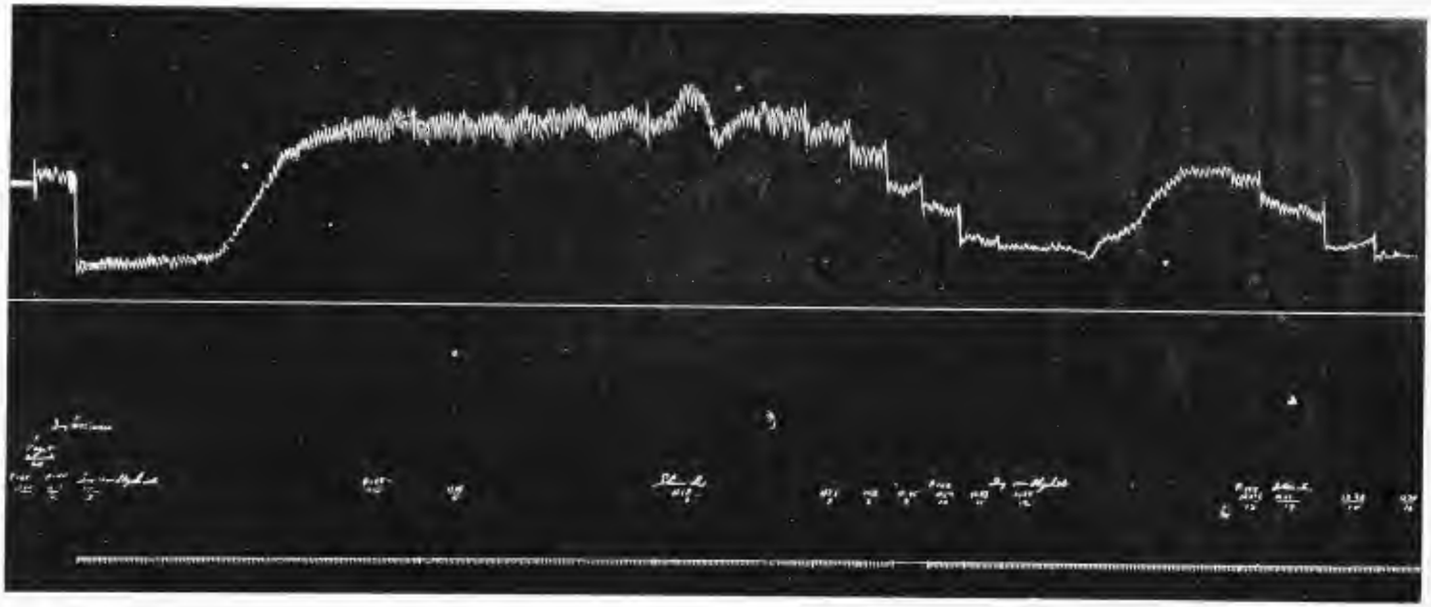


Fig. 33.—Effect on the Blood-Pressure of the Injection of Strychnin into an Animal in a Moderate Degree of Shock.

After both vagi and accelerantes were severed, the animal was reduced to *moderate* shock, then curarised. On injecting a physiologic dose of strychnin the blood-pressure rose much higher than the normal, and after becoming irregular fell to about the level it was before the injection. Note the shorter curve following the second injection, while the third injection caused no change. Then on stimulating the sciatic nerve no rise followed.

neither afferent nor efferent impulses of any kind can pass; hence no injury of an area thus protected can cause even the slightest degree of shock.

We found that no shock could be produced by operations on the extremities if they were performed bloodlessly, and the nerve-trunks had been 'blocked' by local anesthesia, for no afferent impulses could pass the 'block,' and even the amputation of a leg produced no more effect than would be produced by cutting the hair.

These experimental observations have been extensively confirmed in the clinic, in which the use of local anesthesia in the operative field prevents shock from operative trauma. It was soon found, however, that the psychic factor incident to major operations was frequently of great importance. This was strikingly true of operations for exophthalmic goiter. In these cases we often found the psychic factor sufficiently powerful to overwhelm the patient, so that in some cases a raging metabolism, delirium, and death were due to the emotional factor alone.

II. Exhaustion and Shock-Producing Effects of Interference with the Vaso-Motor Mechanism

There is sufficient evidence at hand to make it appear that shock in operations within the splanchnic area is in part, at least, due to disturbance of the local splanchnic vaso-motor mechanism. However, while the splanchnic vaso-motor mechanism plays an important part, that it is not the only factor in the production of shock in these operations is proved by the following observations:—In animals in which the splanchnic blood-vessels had been eliminated, either by clamping the thoracic aorta or by clamping all the splanchnic arteries retro-peritoneally, extensive and continuous manipulation caused the intestines to become paler than normal, and the veins to become comparatively empty. *No immediate fall in blood-pressure followed the trauma* as was the case in other experiments (Fig. 35). *Nevertheless trauma of this area with the blood supply controlled did cause fatal shock,* although not as readily as in cases in which the splanchnic arteries had not been clamped. The blood-pressure did not decline as rapidly as under normal conditions, but the respirations were no less affected than under normal conditions. The respiration became gradually more shallow and usually failed before the heart, which grew gradually weaker and finally failed—the resultant death being independent of the splanchnic vaso-motor factor. It was observed, however, that animals with excluded splanchnic circulation could endure much more splanchnic injury than intact animals.

It is, then, safe to assert that these 'excluded splanchnic-circulation'

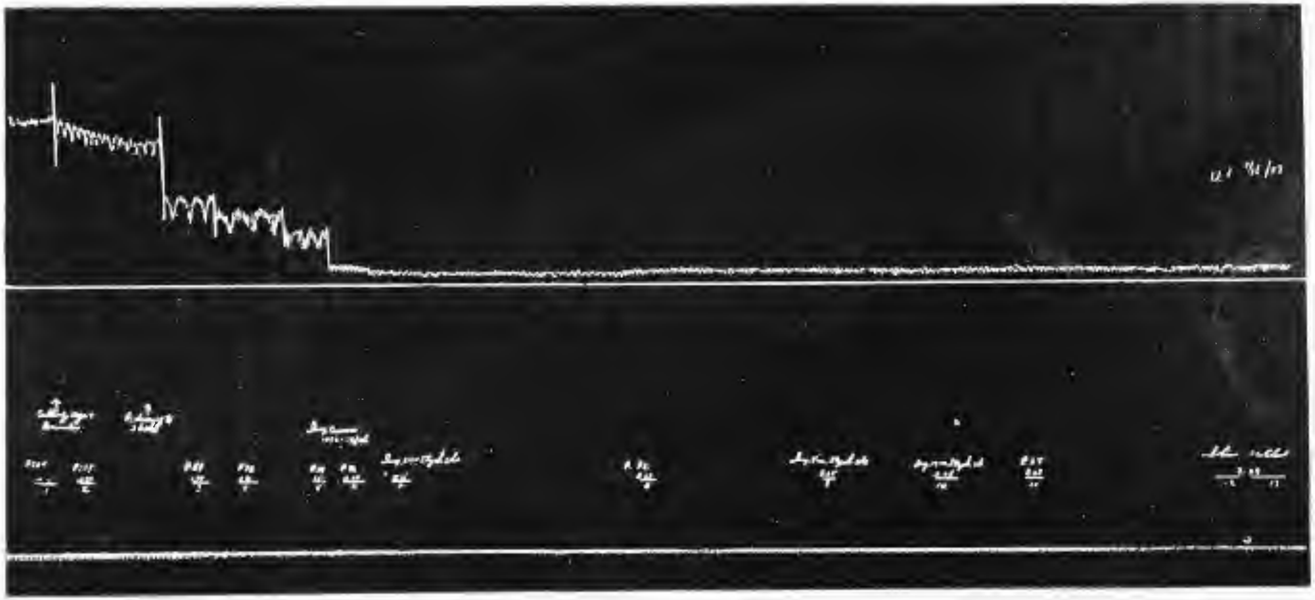


Fig. 34.—Effect on the Blood-Pressure of the Injection of Strychnin into an Animal in Profound Shock.

Both vagi and accelerantes were severed; then the animal was subjected to the usual technic for the production of shock, which appeared as in control experiments. After the shock had become profound, the animal was curarised. Then on burning the paw and stimulating the sciatic nerve and administering physiologic doses of strychnin intravenously, no rise in blood-pressure was noted. Neither did asphyxia cause a rise.

experiments prove that the splanchnic vaso-motor mechanism plays but a part in the production of shock even in such injuries as involve only its own area. There is no evidence which tends to show that the splanchnic factor plays a special part in shock due to operations within any area of the body excepting the splanchnic or genito-urinary area. The rôle of the splanchnic area is probably of but little, if of any, more importance than that of any other area of like vascular capacity. Autopsies in experiments in which the splanchnic area was

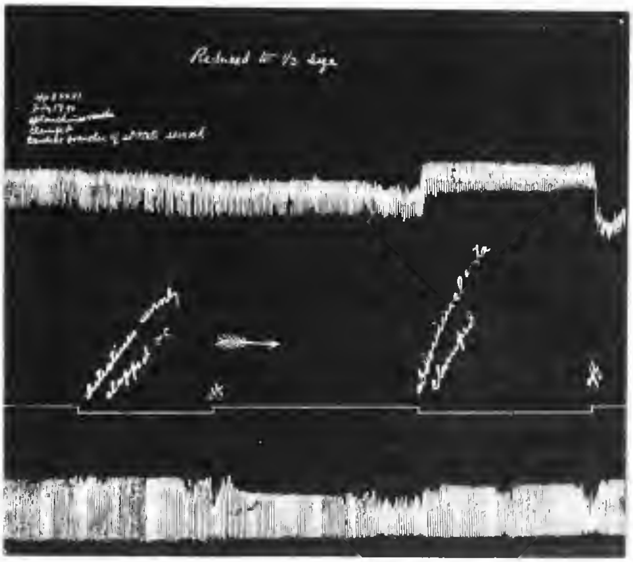


FIG. 35.—Effect on the Blood-Pressure and Respiration of Intestinal Manipulation after Clamping the Splanchnic Vessels and the Aorta.

Upper tracing, blood-pressure. Lower, respirations. Splanchnic arteries clamped and stellate ganglia removed previous to taking this tracing. 1. No effect noted on severe injury of the intestines while freely exposed. 2. Clamping abdominal aorta ; note sustained rise without usual compensatory fall when similar procedures are done with open arteries and intact stellates.

not involved showed that *the vascular distention in this area did not differ from the vascular distention in other areas.*

The following observations are pertinent :—In our experiments on normal animals the first injury, or at least one of the early injuries or stimulations of a nerve-trunk, always produced a rise in blood-pressure ; but after the animal had become well exhausted, trauma or nerve stimulation of nerve-trunks caused little or no rise in the blood-pressure ; in fact, in many instances the blood-pressure fell.

This point has a direct and important bearing upon the conduct of surgical operations, *i.e.* these experimental observations show that the duration of an operation and the amount of tissue surgically injured bear a direct relation to the degree of exhaustion, *unless the field of operation is blocked by local anesthesia.*

The relation between the condition of the patient and the duration and the magnitude of the operation is influenced also by the inhalation anesthetic. This point will be considered in detail in other sections.

After an animal had been reduced to the condition in which stimulation or injury produced a primary fall in blood-pressure instead of the primary rise, which resulted when the animal was fresh, it was found to be practically impossible to raise and sustain the blood-pressure by therapeutic measures. The venous pressure had become so low that the heart received but little blood. The vaso-constrictor mechanism was inactive, except in response to the most heroic stimulation, and even then the temporary gain was followed by a still greater diminution of the blood-pressure.

A number of extensive dissections were made to observe the condition of the vessels at this stage. The arteries were quite empty, the tissues pale, but the larger venous trunks were full, alike in the somatic and in the splanchnic areas. The blood was dark-coloured. In later researches, the cause of this dark colour was found to be blood acidosis.

Operations whereby the fourth ventricle was exposed bloodlessly, or at least nearly so, were attended by most profound vaso-motor disturbances, and the vaso-constrictor or pressor action was soon lost by the mere exposure of this region to the air. If the vaso-motor centre is exposed and cocain dropped on it, the blood-pressure falls to about 50 or 60 mm. In this condition, apparently no amount of trauma produces shock. The coincidence of the lack of response in the blood-pressure-raising mechanism on the application of an adequate stimulus in these cases, in which the vaso-motor mechanism is known to be exhausted, strongly supports the theory of vaso-motor fatigue in traumatic shock.

The results of the experiments with strychnin already noted, in particular the facts that both strychnin shock and traumatic shock caused exhaustion of the vaso-motor mechanism; that exhaustion could be initiated by trauma and completed by strychnin and *vice versa*; *and that when the vaso-motor centre and the spinal cord were first cocainised, neither trauma nor strychnin could raise the blood-pressure in an otherwise normal animal*—these facts in addition to the other experimental findings reported above lead to the conclusion that the vaso-motor mechanism is exhausted in shock. Nevertheless, as will be shown later, exhaustion of the vaso-motor mechanism is not the only factor in the production of shock.

In 103 of the experiments in which the exact manner of death was recorded, or in which in the course of experiments either the heart or the respiration failed first, respiration alone failed in ninety, the heart alone in four, and both simultaneously in nine. In many instances the heart was beating strongly and the blood-pressure was fair at the time respiration failed. Artificial respiration was frequently required during the course of the experiments. The greater the extent of the dissection, and especially if dissection had been made in the thorax or the abdomen, the more readily the respiration became exhausted. In bloodless amputations of the hip-joints and in other mutilating experiments, respiratory failure occurred first. Almost every injury which affects the circulation caused respiratory changes, usually more striking than the vascular changes, and in many experiments, notably in the splanchnic area, the respiration was more affected than was the circulation. When the brain was traumatised, the respiration was strikingly more affected than the circulation, the immediate cause of sudden death from traumatism of the brain in almost every instance being failure of the respiration, as had previously been shown by Sir Victor Horsley. In one gunshot wound, not even touching the medulla, but imparting to it the percussion of the ball, death was caused by respiratory failure. Gunshot wounds of the chest, when large vessels of the heart were not penetrated, caused death by respiratory failure. In laryngeal operations and injuries, respiration was very easily inhibited. In almost every instance of dangerous anesthesia, the respiration was most affected, and frequently stopped suddenly. The heart could be depended upon to continue beating long enough to establish artificial respiration.

There remain other phenomena whose explanation is not attempted on the basis of these experiments; nor is the evidence thus far reported sufficient to explain the mechanism of the vaso-motor failure, or of the respiratory failure, or the general symptoms not due solely to the factor of anemia. Nor does the evidence thus far reported offer any explanation of the action of emotion, of exertion, of infection, of ether anesthesia, of asphyxia, of hemorrhage, as predisposing or contributing causes of exhaustion. These factors were made the subject of other researches, the findings of which will be discussed presently.

Post-Mortem Appearances.—Autopsies were made in a large number of animals, and in general the following conditions prevailed. The large venous trunks were full, the arteries empty, the veins of the splanchnic area not more distended than those of the somatic, unless the experiment had included some procedure in the splanchnic area; the left ventricle and the left auricle were empty, or nearly so; the right auricle usually contained some blood, the right ventricle, little or none; the lungs were anemic; the pulmonary vessels were

empty; the tissues of the brain and of the somatic area were anemic; the liver was usually engorged; the spleen and kidneys somewhat less so. In a number of cases the disposition of the blood was observed by making the necessary dissection under anesthesia just before death.

The macroscopic evidence gave no clue to the cause of death from exhaustion or from shock. Obviously at this point in our investigation it had become necessary to open new lines of research to gain a further clue to the biologic principles involved. Up to this point we had established a quantitative relationship between trauma and shock; we had demonstrated that the brain was insensitive to trauma and that its injury caused collapse rather than shock; we had established the fact that less shock was produced by injury of deep protected tissues than by equal injury of phylogenetically exposed tissues; and that shock was most readily produced by injury of those parts which were most richly sown with nerve-receptors; we had found that exhaustion and shock were produced by exposure of the vaso-motor centre to the air; by exposure of the tissues anywhere—subcutaneous, abdominal, chest, brain; and that shock from injury could be prevented by previously blocking the nerves with a local anesthetic. We then proceeded along wholly different lines of investigation.

III. Exhaustion and Shock-Producing Effects of Trauma as Evidenced by Brain-Cell Changes

On the basis of the investigations which we have already reported, we argued that since the vaso-motor centre is fatigued in shock, other parts of the brain were probably fatigued also, and, following the premises established by Hodge in his studies of fatigue in the bee, we argued that the functional alteration of the brain-cells would be accompanied by physical alterations.

To test this hypothesis, in 1900, in collaboration with Dr. D. H. Dolley, we initiated our histologic studies of the brains of animals after traumatic shock. These studies were later extended, in collaboration with Dr. J. B. Austin and Dr. F. W. Hitchings, to include other forms of shock and exhaustion and other organs. The findings of these later studies will be reported in other sections of this chapter.

We found that when physical injury alone was inflicted on normal dogs under inhalation anesthesia, a certain number of the brain-cells showed first a stage of hyperacidity, characterised by hyperchromatism; and later a stage of exhaustion characterised by chromatolysis, by alteration of the nucleus-plasma relation, by rupture of the nuclear and the cell membranes, and finally

by disintegration (Fig. 36).[1] These changes were most marked in the cerebellum and the cortex and were present also in the medulla and the cord.

Of great significance is the fact that the brain-cells showed no change when the trauma was limited to territories disconnected from the brain by severing the spinal cord, or by local anesthetisation. This finding was anticipated, because we had shown that in these circumstances trauma caused no shock. When the circulations of two dogs were crossed and but one dog was traumatised, brain-cell changes were most marked in the dog traumatised. Dogs *over-transfused*—to eliminate the factor of anemia—and traumatised showed brain-cell changes. This indicated the presence of some shock-producing factor other than blood-pressure changes. When the vitality had been previously reduced by emotion, by physical exertion, by toxins, by infection, by hemorrhage, by excessive thyroid feeding, by adrenalectomy, or by any cause that reduces the vitality, greater brain-cell changes were found after equal trauma, the endurance of the animal being in proportion to its vitality at the beginning of the experiment. We found that trauma under curare caused no more brain-cell changes than approximately equal trauma under ether.

From these observations we concluded that ether anesthesia offers no protection to the brain-cells against the effect of trauma, and that the *lipoid-solvent* anesthetics probably break the arc which maintains consciousness beyond the brain-cells somewhere in the *efferent* path, perhaps at the synapse.

[1] Since accurate observations depended upon the establishment of a standard of cell classification, a method of making differential cell counts was devised by Dr. Hitchings, and the following arbitrary classification adopted by Dr. Dolley and Dr. Austin :

Stage 1.—The so-called hyperchromatic stage. The changes consist essentially in an increase in the chromatic material, both diffuse and in formed masses. The increase is not confined to the cytoplasm, but also occurs in the nucleoplasm. (Fig. 36 A.)

Stage 2.—The normal average amount of chromatin is present in the cell body, but it is beginning to disappear from the dendrite. Except for the latter change this represents the practically normal cell. (Fig. 36 B.)

Stage 3.—There is well-marked disappearance of the chromatin. The tendency of that which remains is to collect peripherally in both the cytoplasm and the nucleoplasm. The cell and the nucleolus are somewhat swollen. (Fig. 36 C.)

Stage 4.—The chromatin has almost entirely disappeared from the cytoplasm, which is beginning to show signs of disintegration. (Fig. 36 D.)

Stage 5.—Except in the nucleolus there is no chromatin inside the nucleus, and very little outside. Vacuolisation and disintegration of the cytoplasm is very apparent. (Fig. 36 E.)

Stage 6.—The chromatin in the nucleolus is all that is left. The nucleoplasm is vacuolated. (Fig. 36 F.)

Stage 7.—The chromatin in the nucleolus is passing out into the cytoplasm. The nucleoplasm is still further degenerated. (Fig. 36 G.)

Stage 8.—The process of disintegration is carried still further. (Fig. 36 H.)

Stage 9.—The chromatin has disappeared even from the nucleolus. The nuclear membrane has almost disappeared. The cell membrane is extensively ruptured. The cell is dead. (Fig. 36 I.)

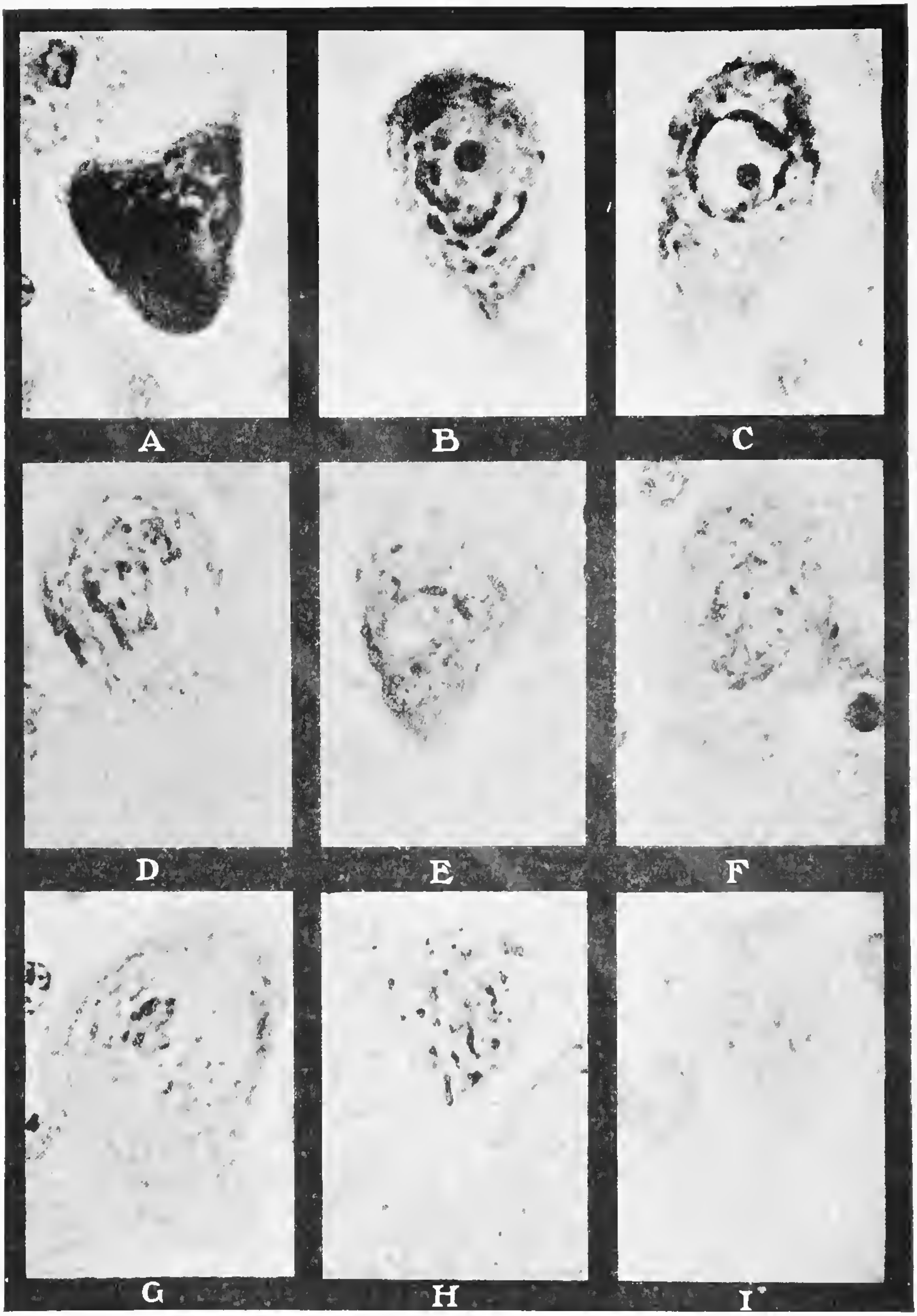


FIG. 36.—Arbitrary Classification of Purkinje Cells. (See footnote, p. 41.)

A. Stage 1.	F. Stage 6.
B. ,, 2.	G. ,, 7.
C. ,, 3.	H. ,, 8.
D. ,, 4.	I. ,, 9.
E. ,, 5.	

(From photomicrographs, 1640.)

The afferent path from the seat of injury being unbroken, the afferent stimuli reach and modify the brain-cells as readily as if no anesthetic had been given, and it would seem that the brain-cell changes must be due to the response of the brain as if in a futile effort to escape from the injury.

Having established a tangible pathology of one type of exhaustion and shock—that produced by trauma—we then took up other types in sequence, beginning with hemorrhage, since hemorrhage — anemia — predisposes to shock. Complete anemia produces death. We therefore evolved a method of resuscitation, and were then in a position to study the effects on the brain and on other tissues of periods of complete and of partial anemia ; and to discover how long the various organs and tissues could endure complete anemia and recover.

IV. Functional and Brain-Cell Changes in Anemia and Resuscitation of the Central Nervous System

In collaboration with Dr. D. H. Dolley animals were killed in various ways, usually by chloroform, then resuscitated by the infusion of adrenalin in an artery—the stream directed toward the heart, and finally killed again for histologic study. Permanent and complete recovery was obtained after five minutes, six minutes, six minutes and ten seconds, six minutes and fifteen seconds, and seven minutes and thirty seconds of total cessation of the circulation (death). That is, one dog out of twelve, with total cessation of circulation for from seven minutes to eight and one-half minutes, recovered : whereas only one out of seven with total cessation of the circulation for from five minutes to six and one-half minutes died, apparently as a direct result of the anemia.[1]

The demarcation between recovery and death was sharp. In practically all the experiments the crisis was reached in from twelve to twenty-four hours. Then death ensued quickly, or else distinct improvement of nervous functions began shortly, and continued more or less rapidly to complete restoration, though in two dogs the convalescent period lasted for four and six weeks respectively.

After six minutes of total cessation of the circulation the narrowness of the escape from permanent death was shown by the degeneration of a certain number of neurons in the recovered dogs, whose brains were studied by the Marchi method. The vaso-motor, the cardiac, and the respiratory centres showed somewhat greater vitality than the higher centres, but the difference

[1] Crile, G. W.: *Anemia and Resuscitation*, 1914.

was not great. In many of the dogs that succumbed after some hours, not only the reflexes but also some of the higher faculties revived.

In general, the following sequence of return of the various functions and reflexes was exhibited: respiration, vaso-motor control, corneal reflex and knee-jerk (tendon reflexes in general), winking, cutaneous reflexes, partial or complete contraction of pupils, and light reflex.

Respiration.—The *respiratory and cardiac* centres showed greater resistance than the *vaso-motor* centres. *Injury or faradisation of the sciatic nerve caused no rise in blood-pressure, indicating loss of vaso-motor tone.* In from ten to twenty minutes after the heart and respiration had again become active the *vaso-motor centres* were reanimated. The vaso-motor restoration was slow in a number of instances. When the blood-pressure rose, indicating a recovery of the vaso-motor centres, then injury or faradisation of the sciatic nerve caused a rise in the blood-pressure. This corresponded well with the relative behaviour of the vaso-motor and the respiratory centres in exhaustion or shock from trauma, for during the progressive failure of the vaso-motor mechanism, the activity of the respiratory mechanism was increased. As the blood-pressure fell, the respiration was increased. It is true that the heart usually continued to beat after final respiratory failure, but the cardiac centres lost their tone before the heart muscle was fatigued.

Blood-pressure.—Depending on the extent of the vaso-motor reactivation, either a tendency to rise was immediately exhibited, or the low level persisted for from ten to twenty minutes, in the latter case with a subsequent rise. Stimulation of the sciatic nerve did not cause the usual rise of pressure until the secondary rise had spontaneously begun and respirations were well re-established.

With one exception, the respiration in all the experiments returned well before the end of the first fall in blood-pressure; that is, before the vaso-motor mechanism was restored. In one experiment as little adrenalin as possible was used; the anemia lasted five and one-half minutes and respiration began two minutes after restoration of the circulation, while reaction to sciatic stimulation was not obtained for four minutes. It appears, therefore, that the return of activity in the vaso-motor centre is nearly synchronous with the return of respiration after shorter periods of anemia, but is more delayed after longer periods. In a puppy subjected to thirty-five minutes of anemia, there was apparently no vaso-motor reactivation.

Temperature.—While not recorded as a matter of routine, sufficient data have been obtained to indicate that the temperature continues to fall for several hours following resuscitation. The lowest rectal temperature was 32·9 degrees C., four hours after anemia of nine and one-quarter minutes, and 33·8 degrees C. was reached sixteen minutes after thirteen and one-third

minutes of anemia. From this point the temperature gradually rose to a state of hyperpyrexia, which was more marked in the animals which succumbed. In the dog which recovered after the maximum period of anemia, the maintained level was reached the second day.

Phenomena referable to the Cerebral Cortex.—Most of the animals which recovered passed through a final stage comparable in many respects to the condition of Goltz's decerebrates. Such a period was characterised by dementia and loss of intelligence, lack of any psychic response to stimuli, and inability to recognise food and drink. Response to stimulation was purely reflex, or was absent if memory of past experiences was involved. For example, meat placed in the mouth was held there passively, or, in one case, forcibly spit out; a flash was answered only by a lid reflex, and there was indifference to the relative position of the forelegs. Power to localise stimuli was gradually reacquired. The clinical observation that the cortex suffered the most and was the last to recover is supported by the fact that the histologic alterations were more marked in the cortex than in the lower centres. This fact also confirms the view that the cytologic state of the brain-cells gives a true indication of their physiologic condition.

Histologic examination both of presumptively recovered animals and of fatal cases was made by ordinary methods and by those of Nissl and Marchi. The neurocytes of the fatal cases uniformly presented the greatest change, some being not merely chromalytic, but in a condition which definitely indicated the death of the cell. Examination by Marchi's method further supported these findings by proving the existence of fibre degeneration. The narrowness of the escape from death of one animal, which four weeks after seven and one-half minutes of anemia had apparently entirely recovered its normal condition, was shown by the degeneration of a number of fibres in the pyramidal fasciculi, which were traced from the cord to the cortex, and in Flechsig's fasciculus, while a more sparsely scattered degeneration of both ascending and descending fibres was evident elsewhere.

The histologic evidence that even in so-called 'recovered' animals, some or even many nerve-cells were permanently lost, and that all were temporarily damaged, explains the great temporary and lesser permanent loss of power following any grave anemia of the brain.

It argues against the practice of permitting the blood-pressure to fall extremely low in cases of hemorrhage before resorting to blood transfusion. It warns the surgeon to be cautious in ligating or temporarily closing the common carotid artery in aged subjects. It warns him not to press on the brain with retractors and packings unless the pressure is made strictly intermittent, never exceeding five minutes at a stretch. It explains why in all types of brain pressure the early depression of the higher functions, such as associative

memory, occurs before the depression of the lower functions, such as respiration and circulation. It emphasises the significance of the gradual onset of dulness and stupor in increased intracranial pressure. It fixes an absolute limit to the possibility of resuscitation in cases of drowning, and therefore makes one doubt the authenticity of many reported cases of resuscitation after apparently long intervals of suspended animation.

Having shown that the lesions in the brain-cells produced by anemia were in certain respects identical with those in shock, we then turned to the study of other predisposing and exciting causes of exhaustion and shock and to an investigation of the restorative powers of sleep.

It is an axiom in the clinic that a patient who does not sleep will make scant or no progress toward recovery. We know that loss of sleep alone is one of the most potent causes of exhaustion; that death will just as certainly result from continuous unbroken consciousness—though it may be longer delayed—as from continuous trauma or from continuous hemorrhage. Are the brain-cell changes produced by prolonged insomnia identical with those produced by trauma and by hemorrhage? Are the cells of any other organs altered? Are the cells thus damaged restored by sleep?

V. Histologic and Functional Evidence of the Exhaustion-Producing Effects of Prolonged Insomnia and of the Restorative Effects of Sleep

INSOMNIA

In collaboration with Drs. Austin and Hitchings, eighty-four experiments were performed, in which rabbits were given abundant food and drink and rest, were kept under ideal conditions, but were not allowed any sleep during continuous periods up to 100 hours in length. The following observations were made:—

(1) Exhaustion developed gradually and was progressive until death.

(2) No agent—sodium bicarbonate, adrenalin, glucose—modified the inevitable exhaustion and ultimate death of the animals.

(3) Death was rather sudden, and without dramatic incident; the machinery of life stopped gradually and quietly, like an exhausted battery.

(4) Temperature, pulse, or respiratory changes were not notable, though there was apparently some decrease in body weight.

(5) The H-ion concentration of the blood remained unchanged until the end.

(6) Microscopic examination of all the principal tissues and organs of the

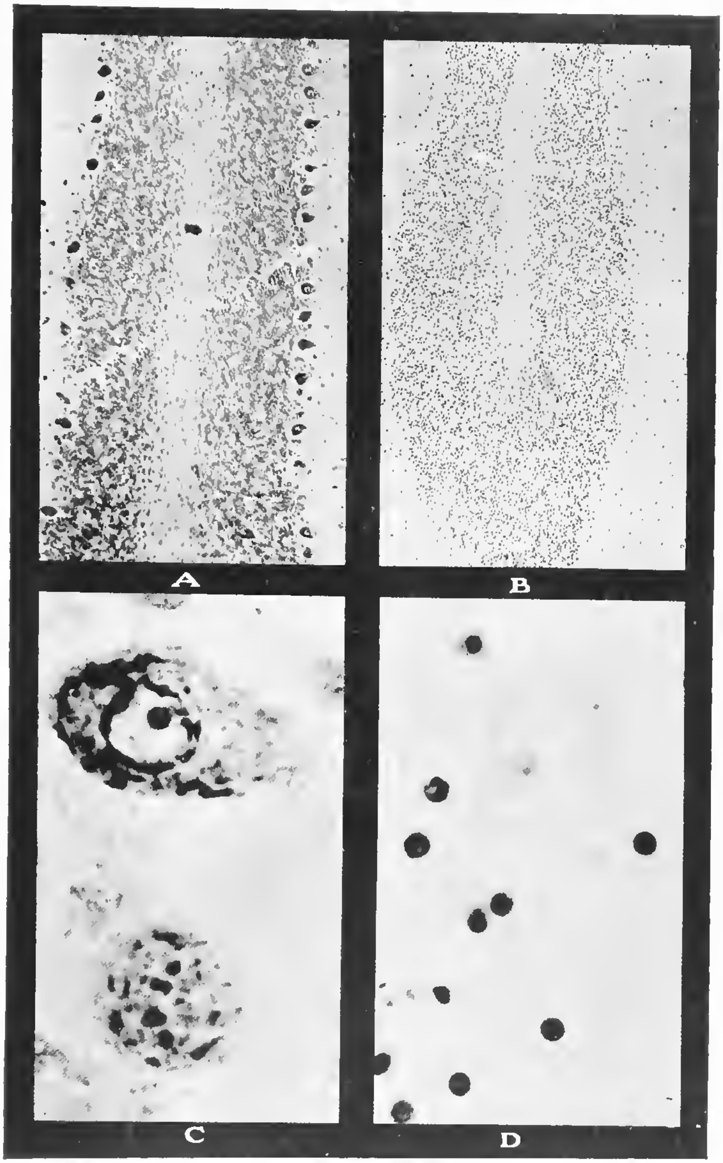


Fig. 37.—Effect of Insomnia on the Brain-Cells of a Rabbit.

A and C, Section of normal cerebellum of a rabbit.
B and D, Section of cerebellum of a rabbit after continuous insomnia for 100 hours.

(A and B from photomicrographs, 100.)
(C and D from photomicrographs, 1600.)

body showed that all were apparently normal, excepting the cells of three vital organs which showed marked changes—the brain, the liver, the adrenals.

Brain.—The changes in the brain were widespread and conspicuous, as evidenced by the photomicrographs (Fig. 37). The changes in the cortex

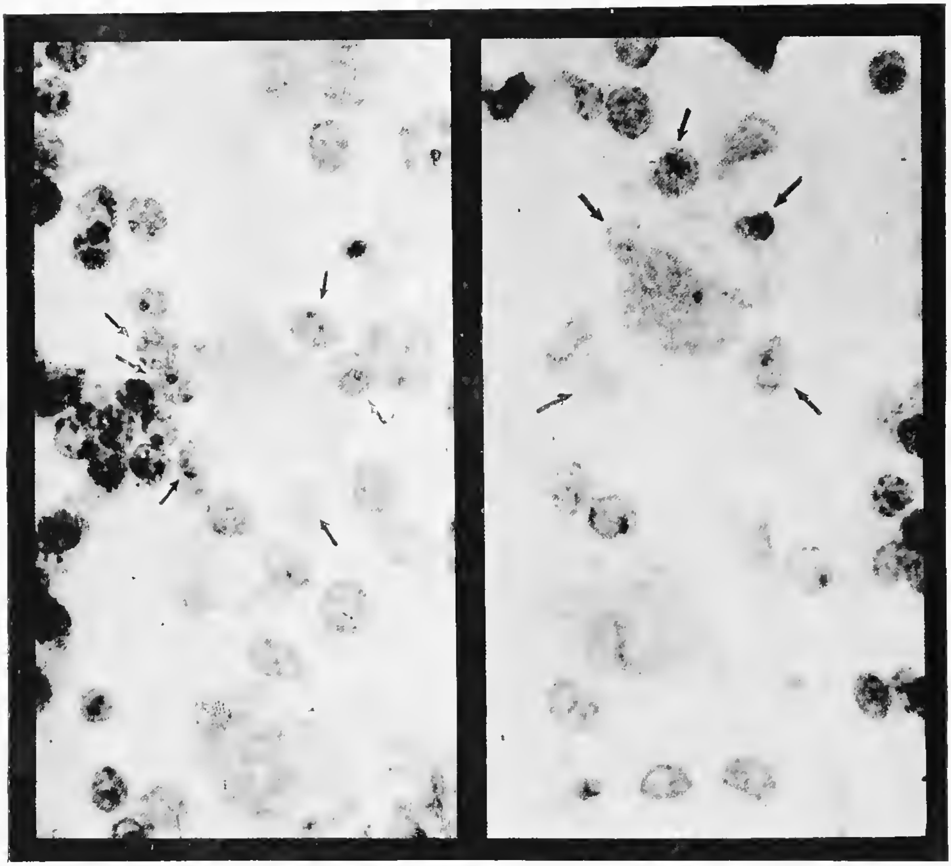


Fig. 38.—Macrophages (see arrows) Surrounding Exhausted Purkinje Cells.

were most marked, in the cerebellum next, and were least marked in the spinal cord and the medulla. One period of sleep restored the brain-cells, excepting those brain-cells whose cell and nuclear membranes had ruptured, and which had lost something which is necessary to make them take a differential stain. These seriously injured cells were followed through to their breakdown and complete disappearance through the action of macrophages (Fig. 38), by making experiments in groups, and killing the animals at various

intervals (Figs. 39 and 40). This gave us the opportunity to follow the complete cycle of cell change through to the end.

Liver.—The cell changes in the liver consisted in the enlargement or swelling of the cells, general disappearance of cytoplasm, the presence of vacuolated spaces, displacement, and occasional disappearance of nuclei. These changes were most marked near the periphery of the lobules (Fig. 41).

Adrenals.—The changes in the histologic structure of the adrenals were most marked in the cortex. In some cases there were marked changes in

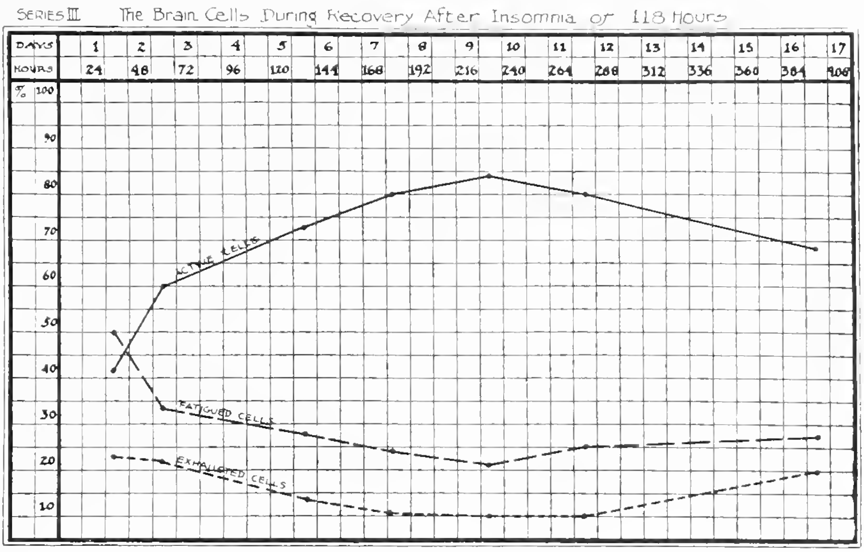


FIG. 39.—Chart Representing the Progressive Changes in the Differential Purkinje Cell Count during Recovery from Insomnia. (See also Fig. 40.)

the cells of the cortex while the cells of the medulla were practically normal in appearance. These histologic changes consisted in enlargement of the cells with occasional rupture of their membranes, distortion of the cell outlines, eccentric displacement of the nuclei, which were often crenated, and general disappearance of cytoplasm (Fig. 42).

SLEEP

A brain-cell which has entered the final stage of disintegration, as evidenced by loss of stainability and rupture of the nuclear membrane, has lost the power of survival and cannot be reproduced. A brain-cell which has reached the stage in which the power of differential staining is lost, has lost the power to

do work. In no instance in 2670 experiments on animals and observations on man have we ever found the power to do work associated with brain-cell changes as marked as those found in the rabbits subjected to these insomnia experiments. Are the swelling, the rupture of the nuclear membrane, and the loss of stainability of the brain-cells due to an intracellular acidosis; and does sleep, by diminishing the work of the brain, do nothing more than give the cells an opportunity to get rid of the acids and to take in alkalis and bases? We attempted to find the answers to these questions by administering large doses of sodium bicarbonate, but no beneficial result ensued. Sleep, therefore, must relate to some other physico-chemical process.

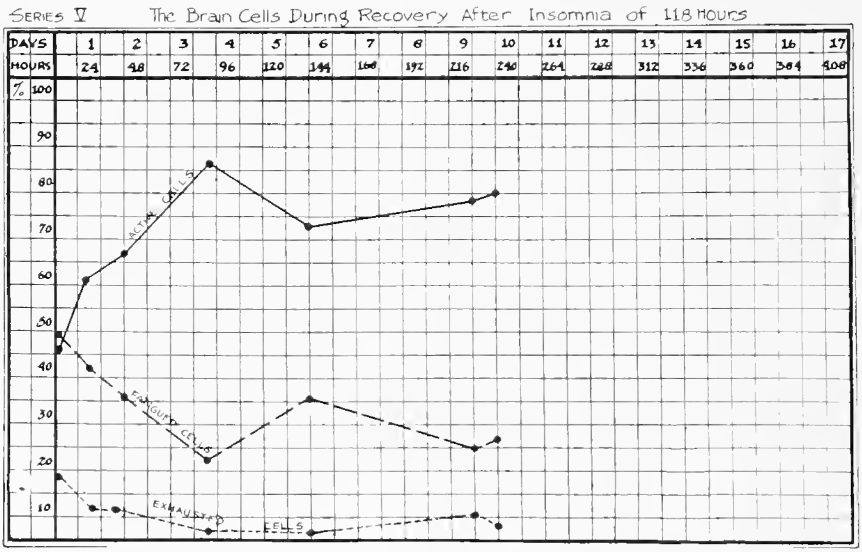


FIG. 40.—Chart Representing the Progressive Changes in the Differential Purkinje Cell Count during Recovery from Insomnia. (See also Fig. 39.)

The histologic evidence indicated that it took many days to restore some brain-cells that were on the verge of final breakdown. There is vast clinical experience as well as supporting histologic evidence that morphin, as a substitute for sleep, accomplishes for the brain-cells much of what is accomplished by sleep. The resemblance of nitrous oxid anesthesia to normal sleep is so marked that in a series of experiments, nitrous oxid was substituted for sleep in the following manner: Animals were kept awake for 100 hours, but were given nitrous oxid anesthesia for one hour out of each six, and during this time the animals were continually moved about so that they could not have fallen into normal sleep. The brain-cells of these animals were preserved

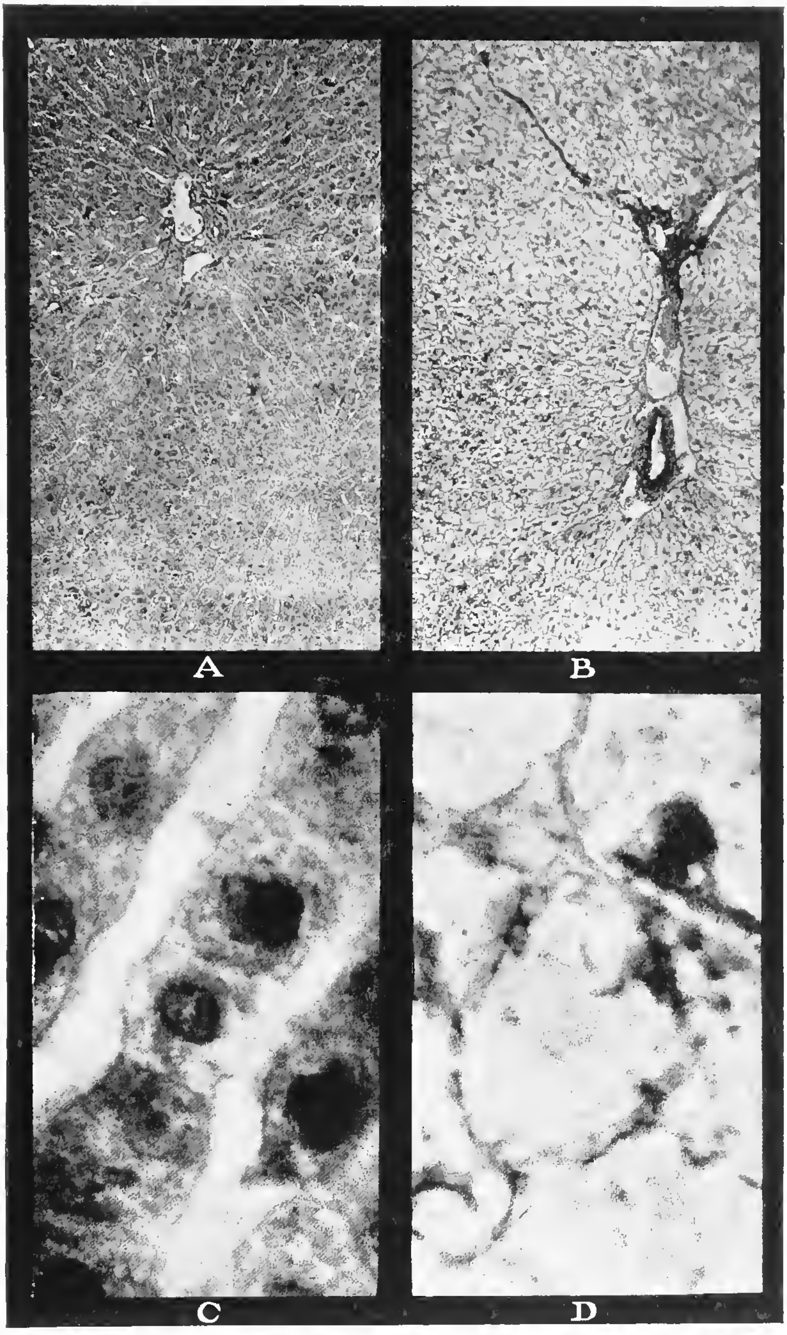


Fig. 41.—Effect of Insomnia on the Liver of a Rabbit.

A and C, Section of normal liver of a rabbit.
B and D, Section of liver of a rabbit after continuous insomnia for 100 hours.

(A and B from photomicrographs, × 100.)
(C and D from photomicrographs, × 1600.)

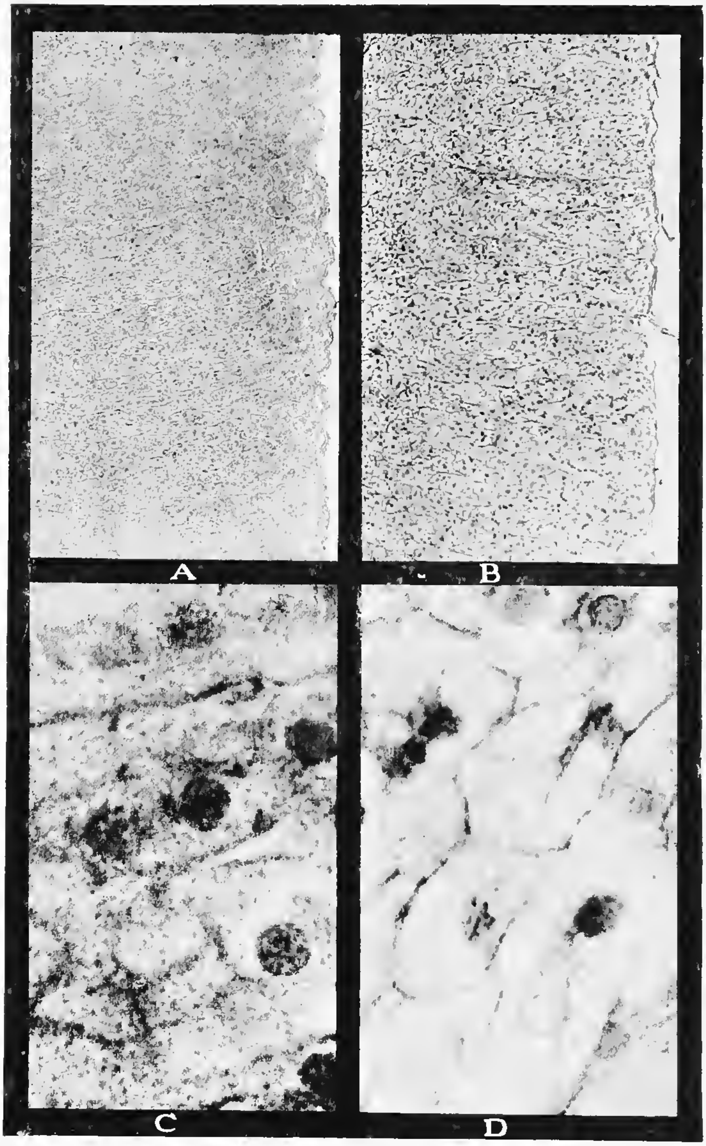


Fig. 42.—Effect of Insomnia on the Adrenals of a Rabbit.

A and C, Section of normal adrenal of a rabbit.
B and D, Section of adrenal of a rabbit after continuous insomnia for 100 hours.

(A and B from photomicrographs, × 100.)
(C and D from photomicrographs, × 1600.)

almost as well as were the brain-cells of others which were allowed like periods of normal sleep (Fig. 43).

In another series of experiments we kept rabbits awake for 100 hours, and

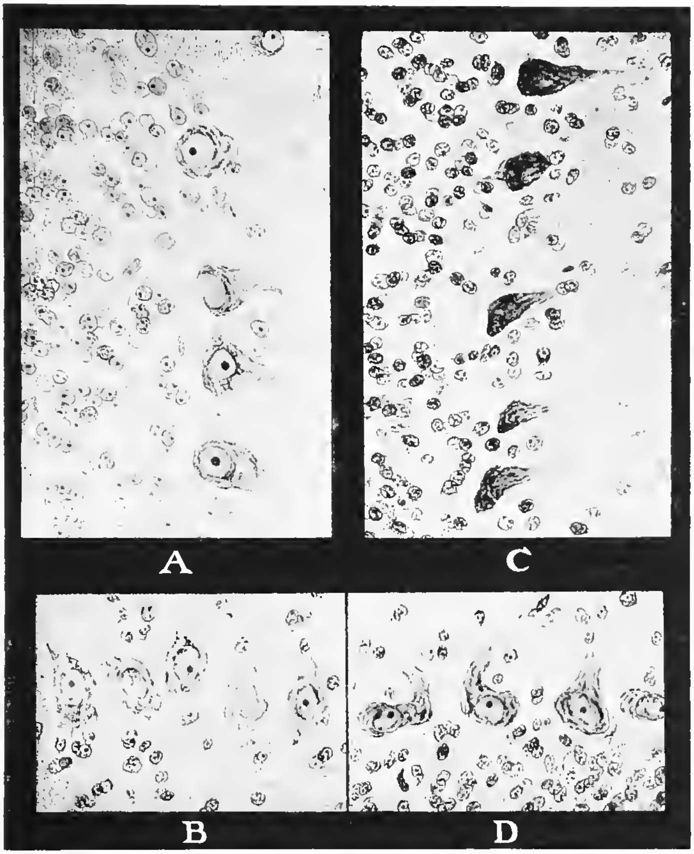


FIG. 43.—Comparison of the Restorative Effects of Nitrous Oxid and of Sleep on the Brain-Cells of Rabbits Exhausted by Insomnia for 109 Hours. (From camera lucida drawings.)

A, Section of normal cerebellum of a rabbit.
B, Section of the cerebellum of a rabbit after continuous insomnia for 109 hours.
C, Section of the cerebellum of a rabbit to which nitrous oxid was administered one hour of each six for 109 hours.
D, Section of the cerebellum of a rabbit which had been allowed to sleep six hours after 109 hours of insomnia.

then subjected some to a seance of nitrous oxid anesthesia, while others were allowed an equal period of normal sleep. The microscopical findings showed that the brain-cells of the animals in both series were restored to the same

degree; but under nitrous oxid the cells of the liver and of the adrenals were not restored to the same degree as were the brain-cells.

We argued that if the restoration of the brain-cells by sleep was a result of lessened work, hence of diminished metabolism, then curare, which inhibits the activity of the vast voluntary muscular system, would reduce the metabolism so greatly that the brain-cells would be restored. To determine this point, such experiments were made in my laboratory by Drs. W. B. Rogers and R. E. Mosiman, with negative results. Still pursuing the 'work' hypothesis, we argued that whereas the total metabolism was diminished by disconnecting the voluntary muscular system from the brain, an agent that would put the brain to sleep might be a substitute for sleep. The work of Meltzer on magnesium sulphate was therefore applied by Rogers and Mosiman, who found that during magnesium sleep the liver cells were considerably restored, but the brain-cells were indifferently restored. We then anesthetised the entire cerebrospinal axis by the intrathecal injection of quinin and urea sulphate, with negative results.

Finally, we turned to the intravenous injection of sea-water in the vain hope that the damaging effect of prolonged consciousness and of other forms of exhaustion might be due to some kind of physico-chemical change that might possibly be overcome by this means. A number of animals were thus treated with indifferent results. Sea-water was tried also in cases of profound shock, with results comparable with the results of other hypertonic solutions.

In our prolonged search for an agent which would act like sleep in the restoration of the exhausted organism, we found that the cells of the brain, the liver, and the adrenals are more restored by opium than by any other agent excepting sleep. Nitrous oxid to some extent effects a like restoration, but is not as potent as opium.

These final results supplied us with the cue to the further study of the problem of restoration, which will be discussed more fully in a later chapter.

VI. Exhaustion and Shock-Producing Effects of Various Agents

EXERTION

Many observations of the effects of exertion were made—including functional and histologic studies of foxes which had been pursued by dogs, of cats which had struggled against restraint, of dogs after a fight, of salmon after their long swim up the Columbia River to the spawning beds, of electric fish after the discharge of their electric mechanism.

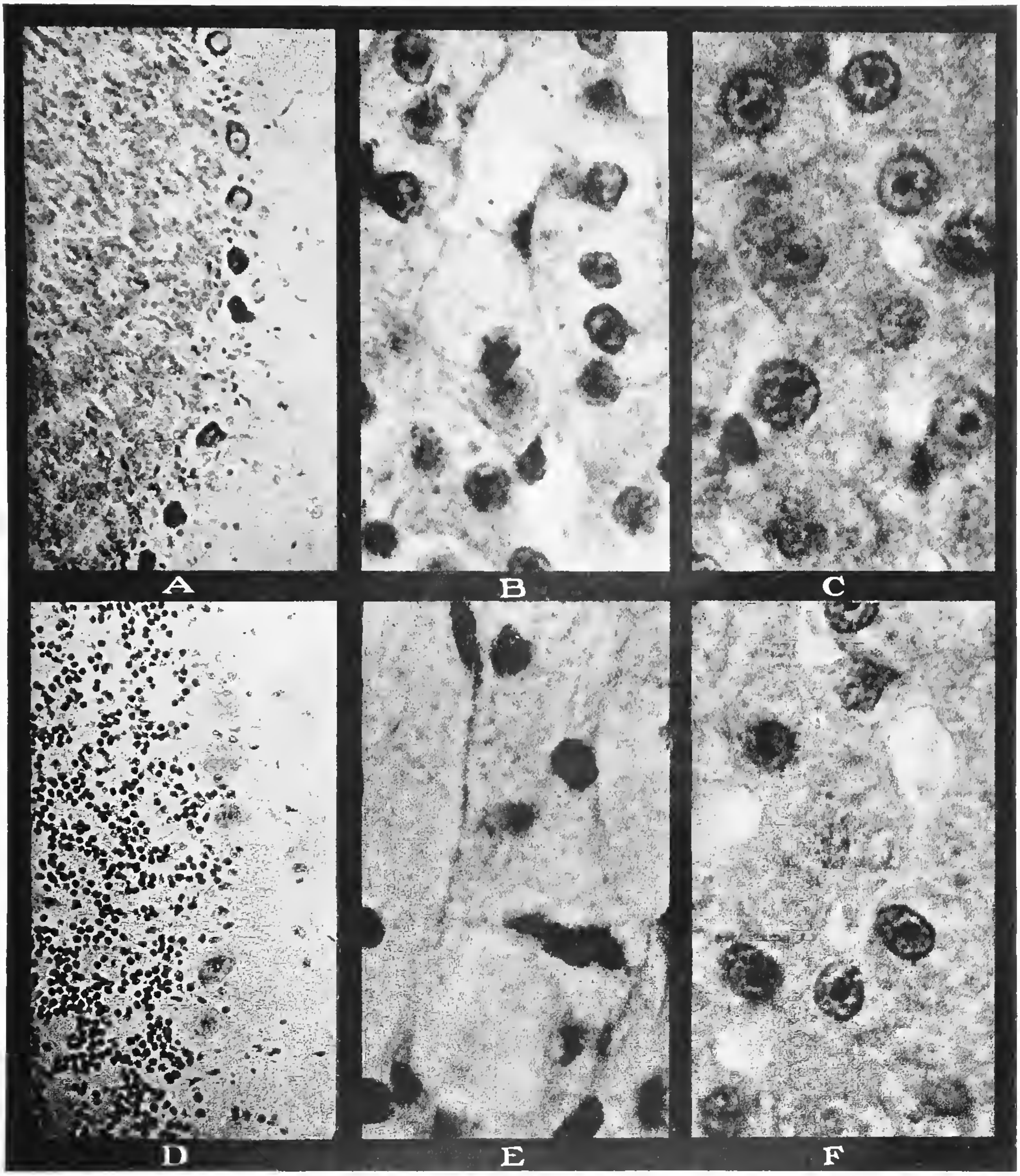


FIG. 44.—Effect of Extreme Exertion on the Brain, Adrenals, and Liver of a Cat.

A, Section of normal cerebellum of a cat.
B, Section of normal adrenal of a cat.
C, Section of normal liver of a cat.
D, Section of cerebellum of a cat after four hours of continuous exertion.
E, Section of adrenal of a cat after four hours of continuous exertion.
F, Section of liver of a cat after four hours of continuous exertion.

(A and D from photomicrographs, × 310.) (B, C, E, and F from photomicrographs, × 1640.)

In the warm-blooded animals, in addition to the obvious phenomena, such as accelerated circulation and respiration, increased temperature, sweating, and final exhaustion, we found in the acute phase of exhaustion increased H-ion concentration of the blood; histologic changes in the brain, the liver, and the adrenals (Figs. 44-47), comparable with those seen in traumatic shock, after

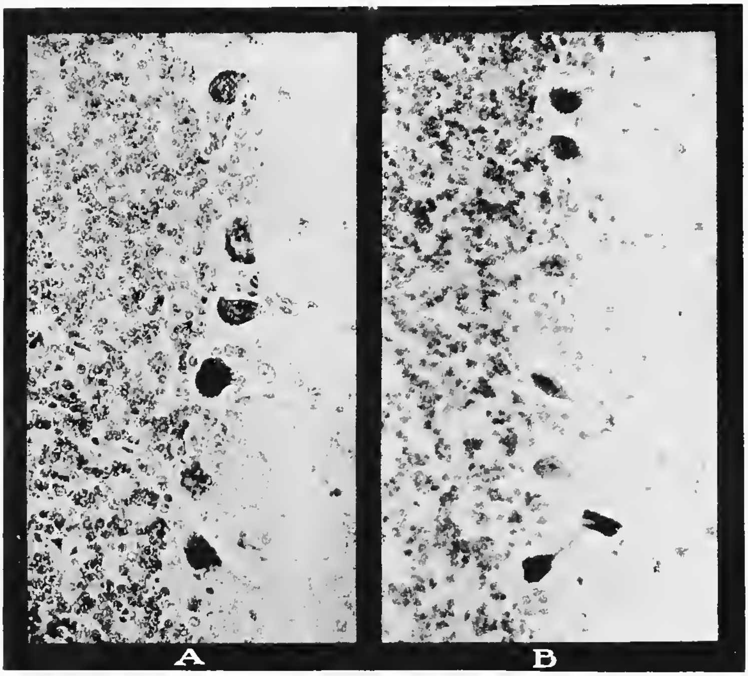


FIG. 45.—Effect of Exertion (Fight and Anger) on the Cerebellum of a Dog.

A, Section of normal cerebellum of dog.
B, Section of cerebellum of a dog killed immediately after a lively fight with another dog.

Note the variations in the chromatism of the cells in B. Compare with the immediate effects of fright in Fig. 18.

(From photomicrographs, × 310.)

the injection of foreign proteins, in infection, and after insomnia; an increased output of adrenalin; an increased iodin content of the thyroid; and a diminished glycogen content of the muscles.

The histologic studies of normally rested salmon taken from the mouth of the Columbia River, as compared with the histologic studies of the salmon exhausted after their long swim of about 1000 miles to the spawning grounds at the headwaters, showed in the latter striking histologic changes in the brain,

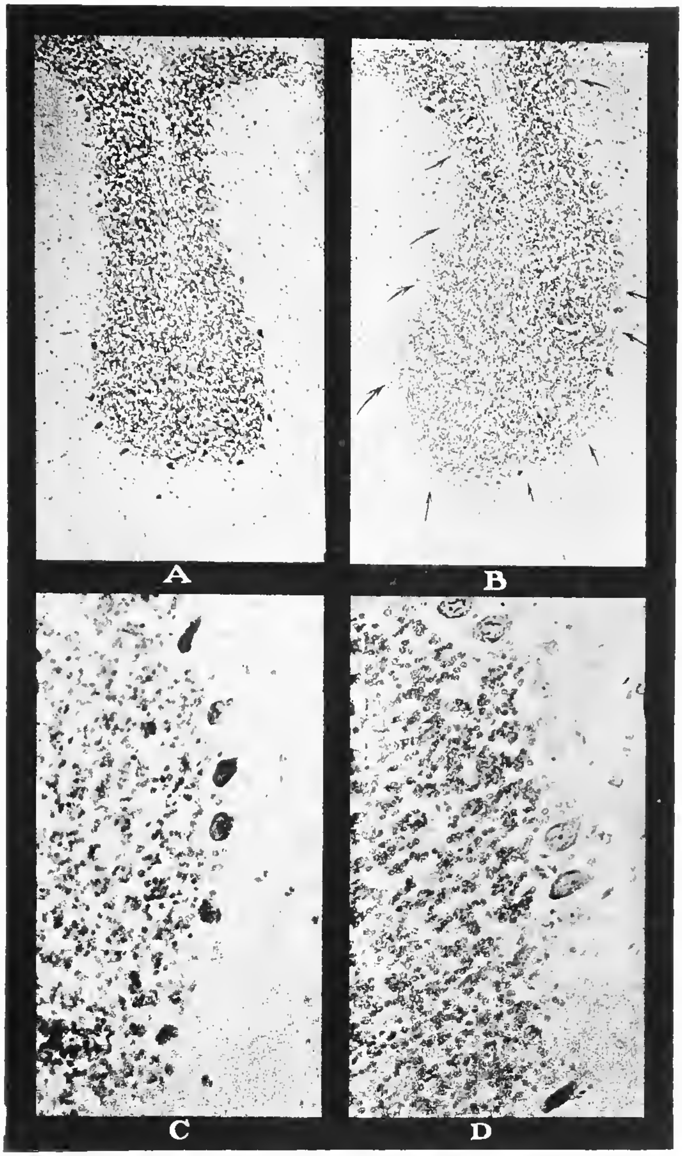


FIG. 46.—Effect of Prolonged Exertion on the Cerebellum of a Fox.

A and C, Section from normal cerebellum of a fox.
B and D, Section from cerebellum of a fox after a 7-mile chase.

The arrows in B indicate the faint traces of Purkinje cells. Compare with the clearly defined cells in A.

(A and B from photomicrographs, × 85.)
(C and D from photomicrographs, × 310.)

the liver, and the adrenals analogous to those seen in other forms of exhaustion (Fig. 48).[1]

Electric fish in the Naples Aquarium and others caught off Cape Hatteras were studied by Dr. M. L. Menten before and after the discharge of their electric batteries. In these a comparison of the cells of the brain, the liver, and the adrenals of the relatively normal electric fish with the cells of these organs in fish which had repeatedly discharged their electric batteries, until they were exhausted, showed in the latter histologic changes analogous to those produced

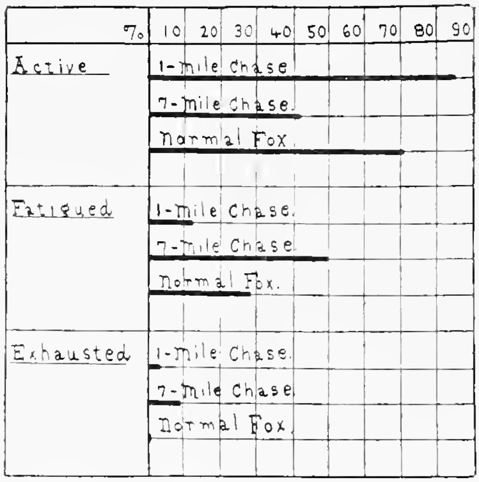


FIG. 47.—Comparison of the Differential Purkinje Cell Count in Normal Foxes with the Purkinje Cell Counts in Foxes after Short and after Prolonged Exertion.

in other animals by insomnia, by physical trauma, and by exertion (Fig. 49). The significance of these observations on electric fish will be made evident in a later chapter in which an attempt is made to associate the electric phenomena of the electric fish with the phenomena of the driving forces of the brain in its response to numerous other forms of energy transformation and exhaustion. In this connection it is of interest to note in passing that the electric discharge of the electric fish was diminished by morphin, was abolished by anesthesia, was immensely facilitated by strychnin; that adrenalin caused hyperchromatism of the brain-cells of the electric fish; and finally, that the statement has been made that food and sleep are essential for the recharging of the batteries of the electric fish.

[1] These specimens were secured through the courtesy of Dr. R. C. Coffey of Portland, Oregon.

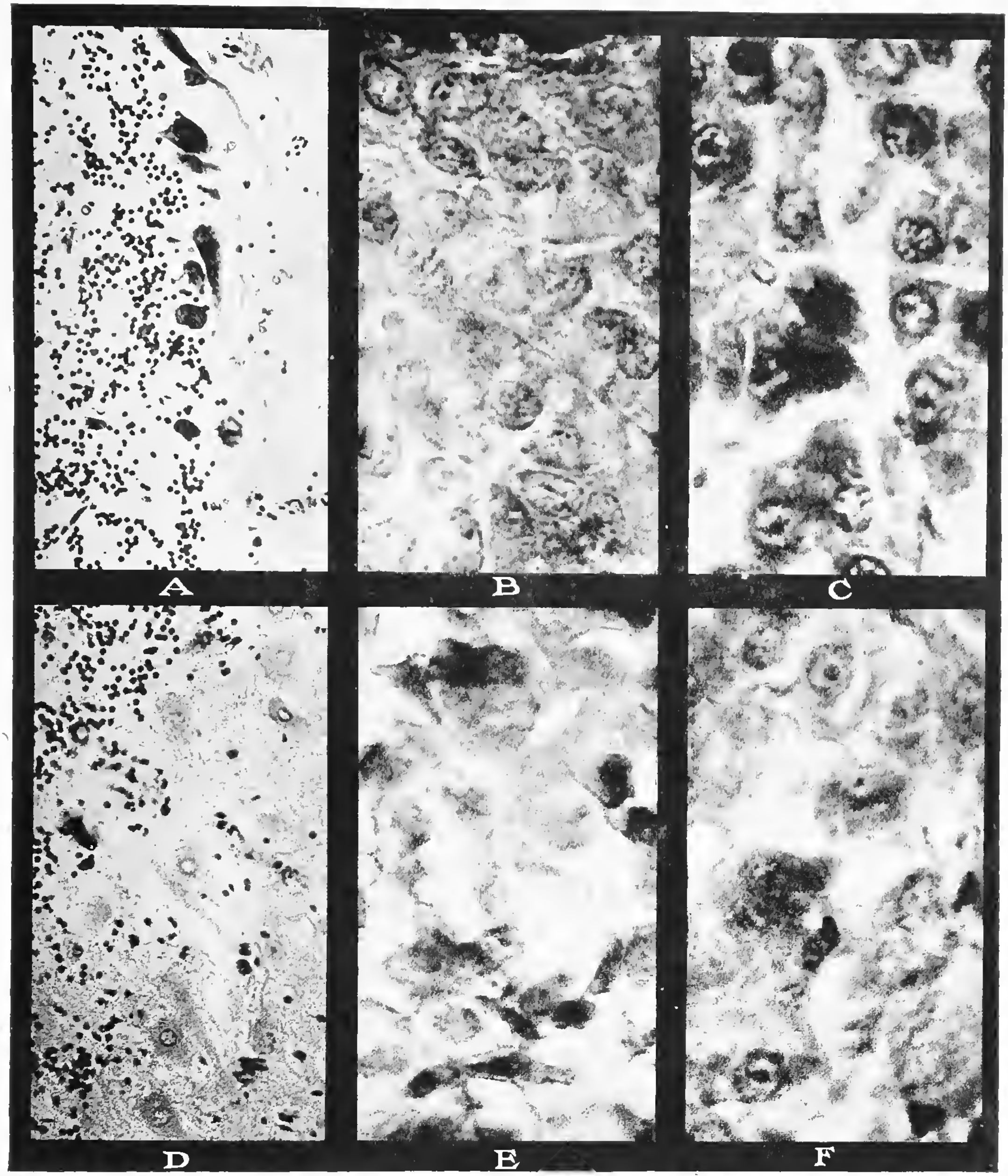


FIG. 48.—Effect of Prolonged Exertion on the Brain, Adrenals, and Liver of a Salmon.

A, Section of cerebellum of a salmon caught at mouth of Columbia River.
B, Section of adrenal of a salmon caught at mouth of Columbia River.
C, Section of liver of a salmon caught at mouth of Columbia River.
D, Section of cerebellum of salmon caught in headwaters of Columbia River after its swim of over 700 miles from the mouth of the river to its spawning ground.
E, Section of adrenal of salmon caught in headwaters of Columbia River after its swim of over 700 miles from the mouth of the river to its spawning ground.
F, Section of liver of salmon caught in headwaters of Columbia River after its swim of over 700 miles from the mouth of the river to its spawning ground.

(A and D from photomicrographs, × 310.) (B, C, E, and F from photomicrographs, × 1640.)

EMOTION

The emotive response of timorous animals is a commonplace. As a human experience it is universal. That it may be graded in intensity up to a critical point is acknowledged; that it may be overwhelming and suspend function is commonly observed. In our researches we used many animals, and found,

A B

FIG. 49.—Effect of Electric Discharge on the Brain-Cells of an Electric Fish.

A, Section of normal cerebellum of an electric fish (× 310). B, Section of cerebellum of electric fish after discharge (× 310).

Note the general disappearance of chromatic material and the almost entire disintegration of some Purkinje cells—indicated by arrows—in B, as compared with the definitely outlined cells of A.

as Colonel Mott[1] has concluded, that the emotive response is one of the most powerful of which the organism is capable. Emotion causes a more rapid exhaustion than is caused by exertion, or by trauma, excepting extensive mangling of tissue, or by any toxic stimulus except the perforation of viscera.

[1] Mott, F. W.: *War Neuroses and Shell Shock*, 1919.

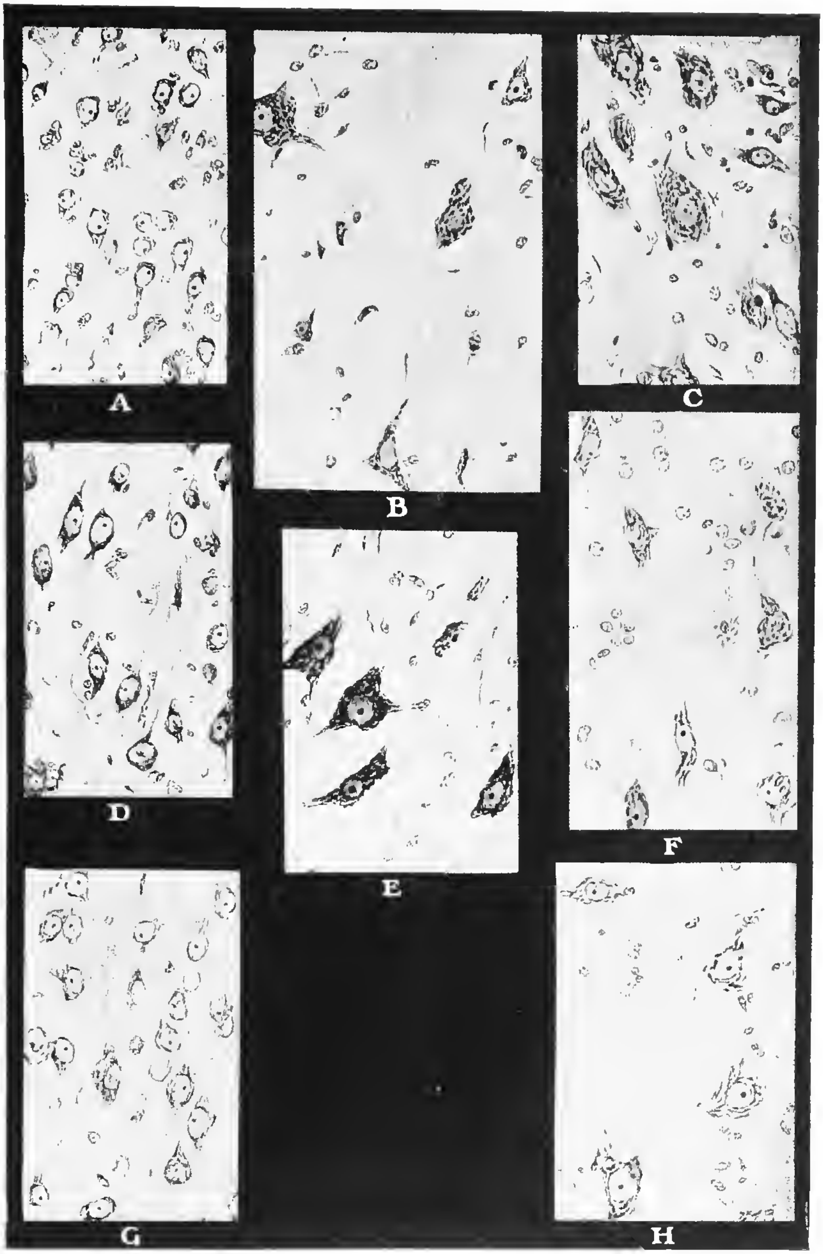


FIG. 50. Immediate and Late Effects of Fright on the Cerebrum, Medulla, and Cervical Cord of a Rabbit. (From camera lucida drawings.)

A, Section of normal cerebrum of a rabbit.
B, Section of normal cervical cord of a rabbit.
C, Section of normal medulla of a rabbit.
D, Section of cerebrum of a rabbit killed immediately after one seance of fright.
E, Section of cervical cord of a rabbit killed after one seance of fright.
F, Section of medulla of a rabbit killed immediately after one seance of fright.
G, Section of cerebrum of rabbit killed six hours after one seance of fright.
H, Section of medulla of rabbit killed six hours after one seance of fright.

Note the hyperchromatic condition in D, E, and F—the *immediate* results of fright, and compare with the loss of chromatic material in G and H—the late results of fright.

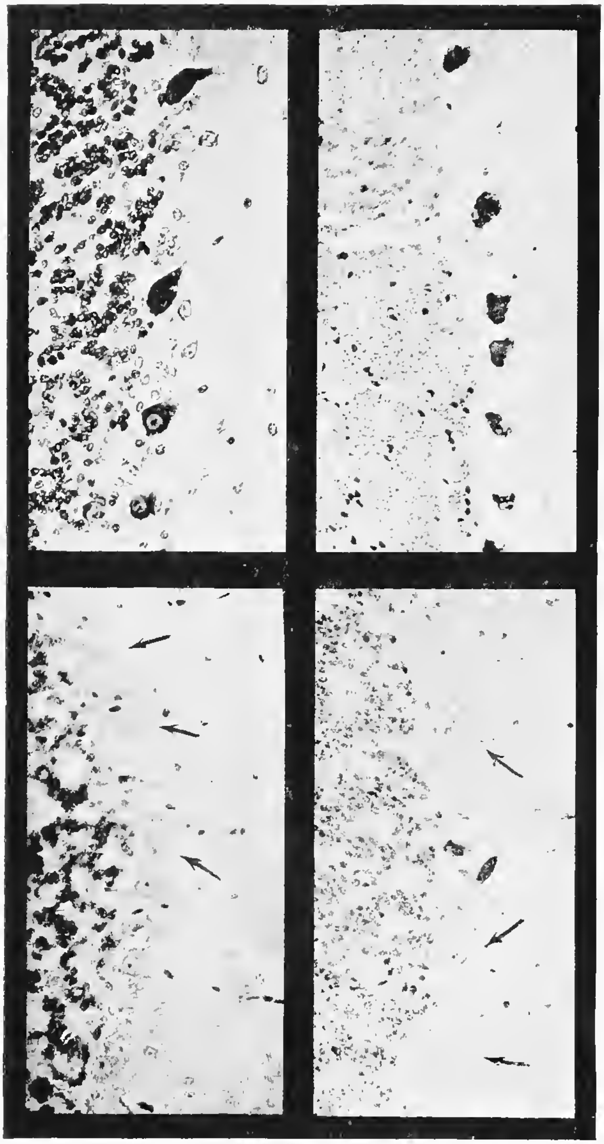


Fig. 51. Effect of Fright, Acute and Chronic, on the Brain-Cells of a Rabbit.

A. Section of normal cerebellum of rabbit (× 310).

B. Section of cerebellum of rabbit killed immediately after 25 minutes of fright (× 310).

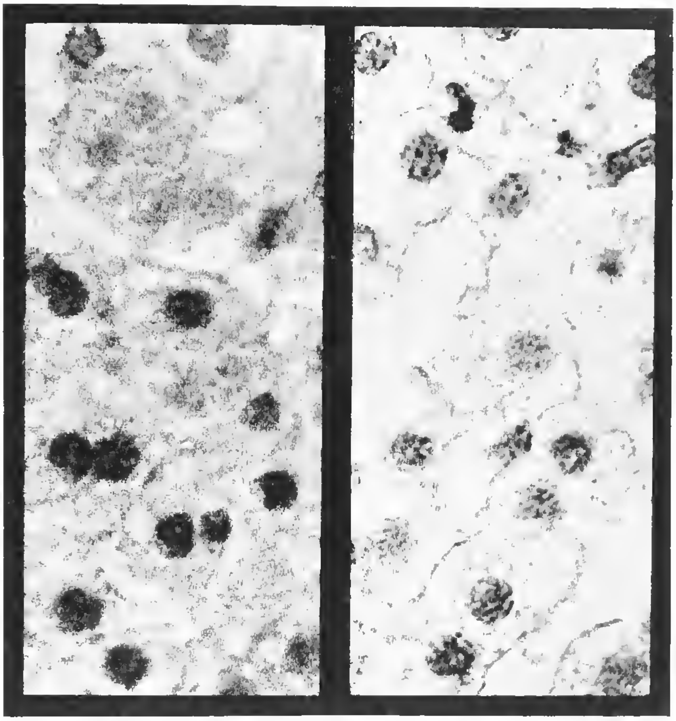
C. Section of cerebellum of rabbit after 10 minutes of fright, killed after $2\frac{1}{2}$ hours of rest (× 310).

D. Section of cerebellum of rabbit frightened twice a day for two weeks (× 310).

In B the first effect of fright is seen in the hyperchromatic condition of the Purkinje cells; this stage of stimulation or mobilisation of energy to meet the increased demand of an emergency being followed by chromotolysis or disappearance of Nissl substance, evident in the cells of C. In D the lasting effects of repeated fright are seen in the high percentage of fatigued and exhausted cells.

Apparently in birds, in particular, the emotion of fear may instantly overwhelm the organism, as when a bird is unexpectedly confronted by a snake.

In metabolism observations made in our laboratory by Major R. D. Milner, the emotion of fear increased the metabolism of rabbits from ten to twenty per cent.



A B

Fig. 52.—Effect of Repeated Fright on the Liver of a Rabbit.

A. Section of normal liver of a rabbit.

B. Section of liver of a rabbit which had been frightened for 20 minutes daily for 45 out of 48 days.

Note the loss of cytoplasm and of nuclei, the swollen cells and the vacuolated spaces in B.

(From photomicrographs, 1640.)

In our experiments, fear caused profound changes in the cells of the brain, the liver, and the adrenals (Figs. 50-54); in some cases the blood was acutely acidosed; in some cases albumin and sugar appeared in the urine; the adrenalin output, as has been demonstrated by Cannon, was increased (Fig. 55); the electric conductivity of the brain, the liver, and of other organs was altered.

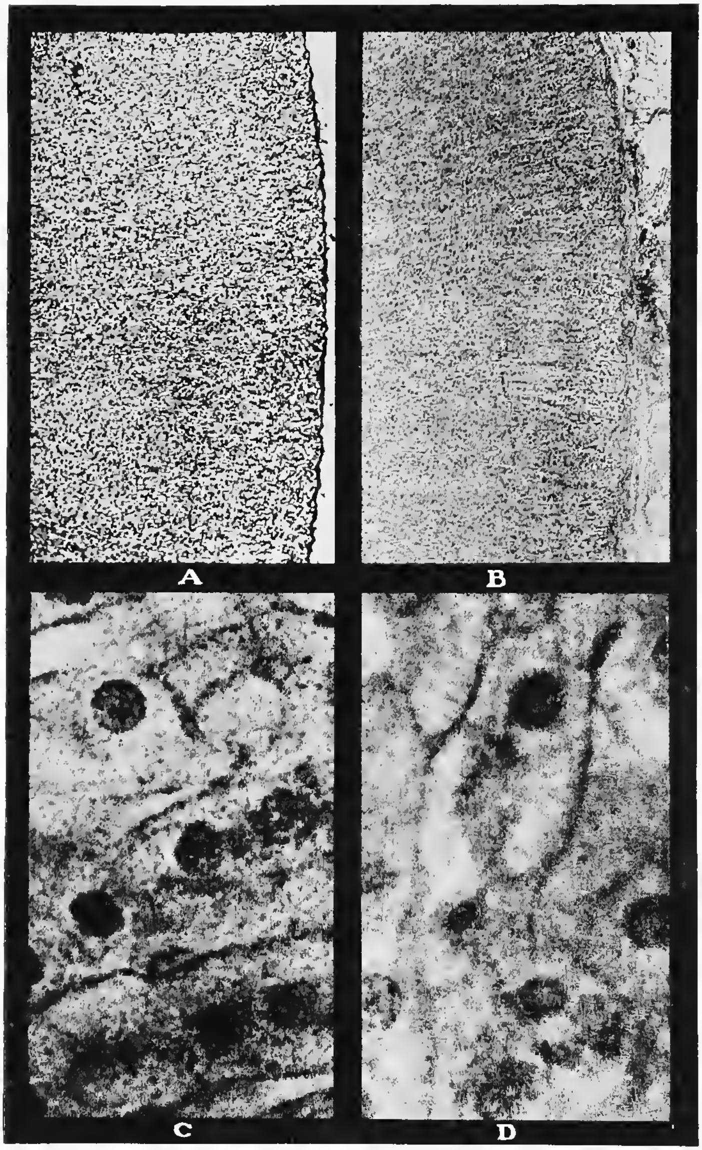


FIG. 53. – Effect of Repeated Fright on the Adrenals of a Rabbit.

A and C, Section of normal adrenal of a rabbit.

B and D, Section of adrenal of a rabbit which had been frightened for 20 minutes daily for 45 out of 48 days.

In B and D note the loss of cytoplasm and of nuclei.

(A and B from photomicrographs, × 85.)
(C and D from photomicrographs, × 1640.)

In short, our researches have shown that the emotions drive the organism with extreme intensity; that, like trauma or exertion, emotion may drive the organism within the limits of normal response, or so overwhelmingly as to suspend the normal functions and reduce the individual to a state of complete cold prostration. In other words, emotion may cause *exhaustion*; it may cause *shock*.

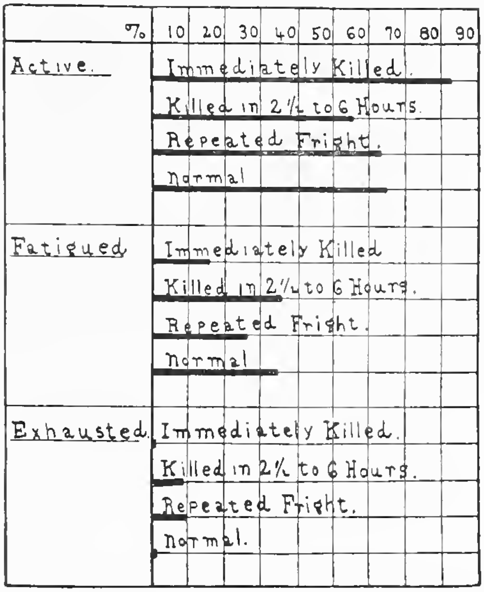


FIG. 54.—Comparison of Differential Purkinje Cell Counts in Normal and in Frightened Rabbits.

This chart shows that fear causes an increase in the number of active cells immediately after fright, which is followed by a decrease in the number of active cells, a corresponding increase in the number of fatigued cells, and an increase of almost 10 per cent. in the number of exhausted cells. After repeatedly frightening rabbits the clinical observation that they soon became accustomed to being frightened is consistent with the fact that no more than 10 per cent. of exhausted cells were found.

INFECTIONS, TOXINS, FOREIGN PROTEINS, ANAPHYLAXIS

In our experiments we found that one effect of the intravenous injection of a foreign protein or of a toxin was early hyperchromatism of the brain-cells followed by chromatolysis. The histologic changes thus produced in the brain, the liver, and the adrenals could not be distinguished from the changes present in any other type of exhaustion (Fig. 56).

A B C

Fig. 55.—Cannon Test for Adrenalin, showing Reaction of the Adrenals to Stimulation—Fear.

A, Control blood negative; no adrenalin present.

B, Positive adrenalin reaction produced by fright of ten minutes' duration.

C, Adrenalin still present, but in lesser amounts under the influence of the longer period of fright. The glands had probably become partly exhausted.

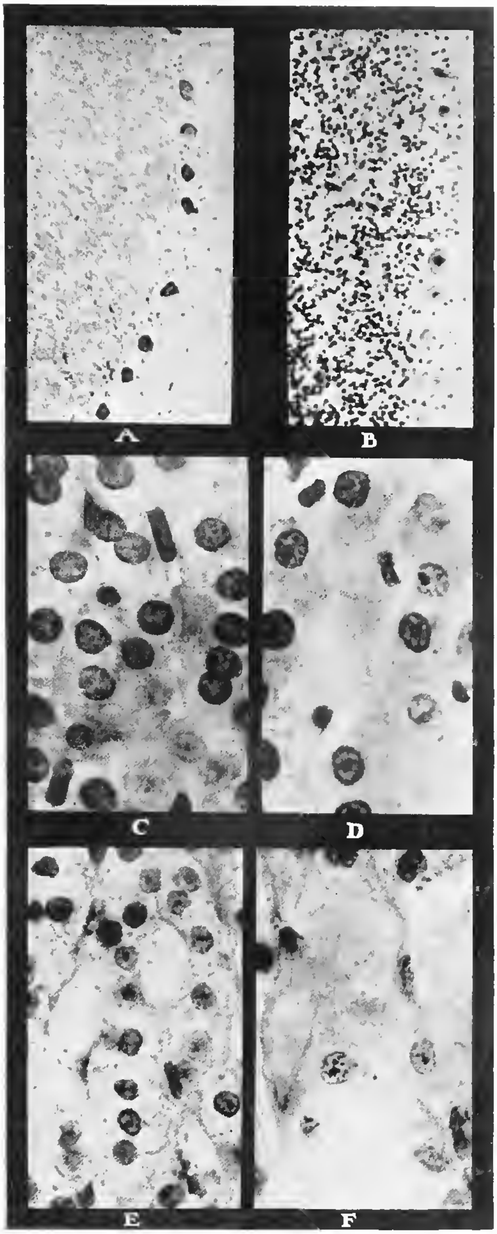


FIG. 56.—Effect of Diphtheria Toxin on the Brain, Liver, and Adrenals of a Rabbit.

A, Section of normal cerebellum.
B, Section of cerebellum after injection of diphtheria toxin.
C, Section of normal liver.
D, Section of liver after injection of diphtheria toxin.
E, Section of normal adrenal.
F, Section of adrenal after injection of diphtheria toxin.

(A and B from photomicrographs, × 310.)
(C to F from photomicrographs, × 1640.)

Studies by Cannon's method showed that the presence of a foreign protein increased the output of adrenalin (Fig. 57). The effect of adrenalin alone in causing the phenomena of fever will be considered elsewhere; at this point, however, it is of interest to note that morphin not only prevented the increased output of adrenalin (Fig. 58), but also measurably protected the brain, the liver, and the adrenals against histologic changes (Fig. 59). These observations

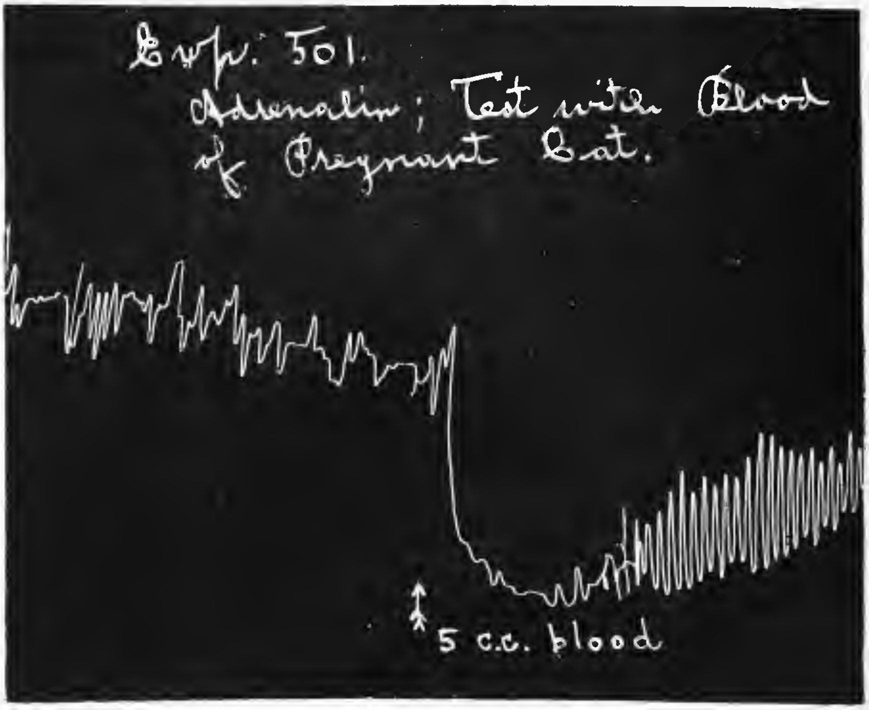
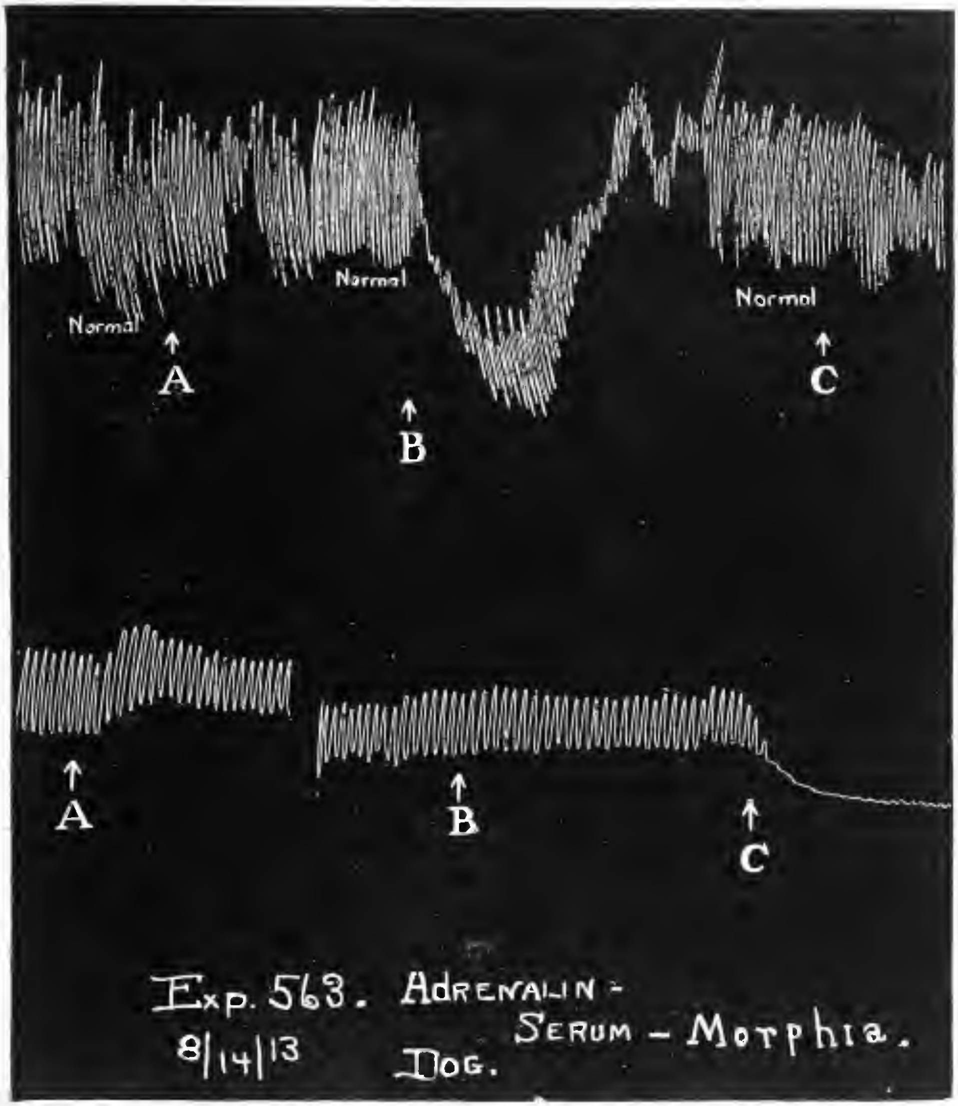


Fig. 57.—Tracing Showing Effect of Pregnancy on the Adrenal Output of a Cat. (Cannon Test.)

That the adrenal glands are activated during pregnancy is positively demonstrated by this sharp inhibition of the contractions of intestinal muscle when the blood of a pregnant cat is substituted for normal blood.

are in harmony with the protective effects of morphin in the presence of infection as seen by the clinician.

As for the response to lighter doses of foreign proteins, there is increased energy transformation manifested by fever, just as the response to light trauma is increased energy transformation manifested by muscular action. If the physical injury or the toxin be overwhelming, then the opposite state is produced—prostration, subnormal temperature. These antithetical results may



B

Fig. 58.—Tracing Illustrating Protective Effect of Morphin in Anaphylactic Shock. (Cannon Test.)

In the upper tracing the adrenalin which appears in the blood as a result of anaphylaxis inhibits the contractions of the intestinal muscle (B, upper tracing).

The lower tracing shows that the injection into a morphinised animal of beef serum, which in the normal animal would have caused a strong anaphylactic reaction and a greatly increased output of adrenalin, causes no increased output of adrenalin, as is evidenced by the contractions of intestinal muscle as in normal blood (B, lower tracing). Since morphin acts directly upon the brain, this experiment evidences not only the protective effect of morphin but also the dependence of the adrenal upon the brain for its activity.

be interpreted as follows :—In the case of intense stimulation—whether by trauma or by toxin—the brain-cells are so overwhelmed and their delicate responsive mechanism is so disturbed that they can do no work. This ultimate condition is shock. Morphin has the power to moderate or prevent the effect of this blow, hence the remarkable protective value of large doses of morphin in the presence of overwhelming stimulation, whether traumatic, toxic, or anaphylactic.

HEMORRHAGE

In sudden death from volume hemorrhage, such as follows the division of the aorta, no histologic changes were seen, but when the hemorrhage was more protracted, especially if a state of low blood-pressure persisted, there appeared cytologic changes in the brain, the liver, and the adrenals identical with those found in other forms of exhaustion. Hemorrhage was always accompanied by acute blood acidosis, and by an increased output of adrenalin. Hemorrhage, therefore, is synergistic with other causes of exhaustion.

COLD AND WET

That depression and fatigue result from long exposure to a humid atmosphere, and from wearing damp and wet clothing, especially in cold weather, is a common experience. Sir Almroth Wright [1] has found that exposure to cold produces acute acidosis in rabbits. In a limited number of experiments in which rats were kept in cold water for varying periods of time, the rats became exhausted, though it was of course impossible to judge to what extent the exhaustion was due to the immersion and to what extent to exertion. Whatever the cause, however, we found the same cytologic changes in the brain, the liver, and the adrenals as those found in exhaustion from other causes.

STARVATION

The clinic supplied us with examples of exhaustion and death due to the effects of inoperable, obstructing malignant tumors of the stomach or œsophagus. Examination of the brains of these cases showed the typical changes of exhaustion.

ASPHYXIA

In cases of suboxidation and asphyxia the outstanding phenomena are *diminished* voluntary muscular activity and *diminished mental activity.* In contrast, however, there is *increased respiratory activity.* If our explanation of

[1] Wright, A. E., and Colebrook, L.: *Lancet*, 1918, i, 763-765.

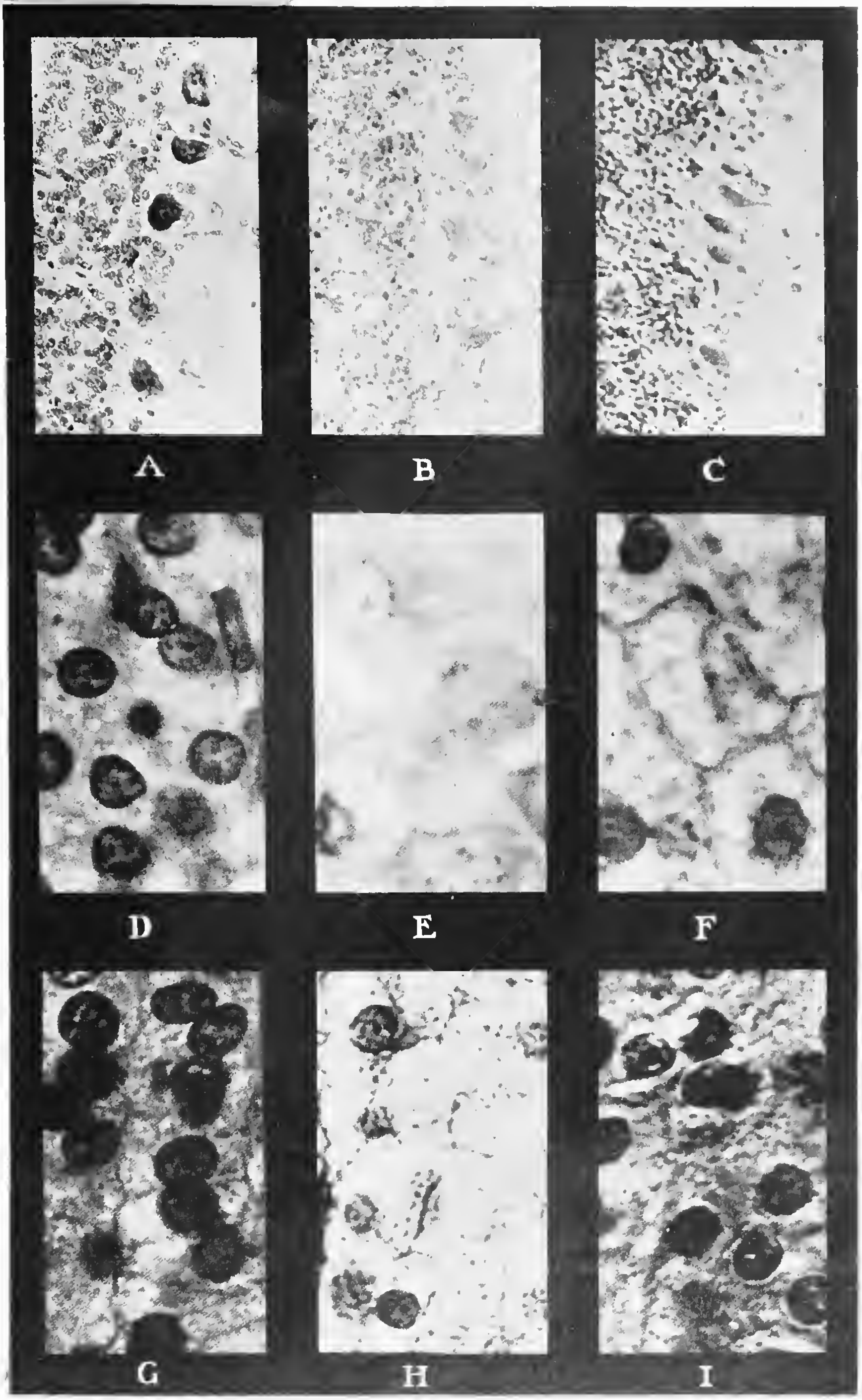


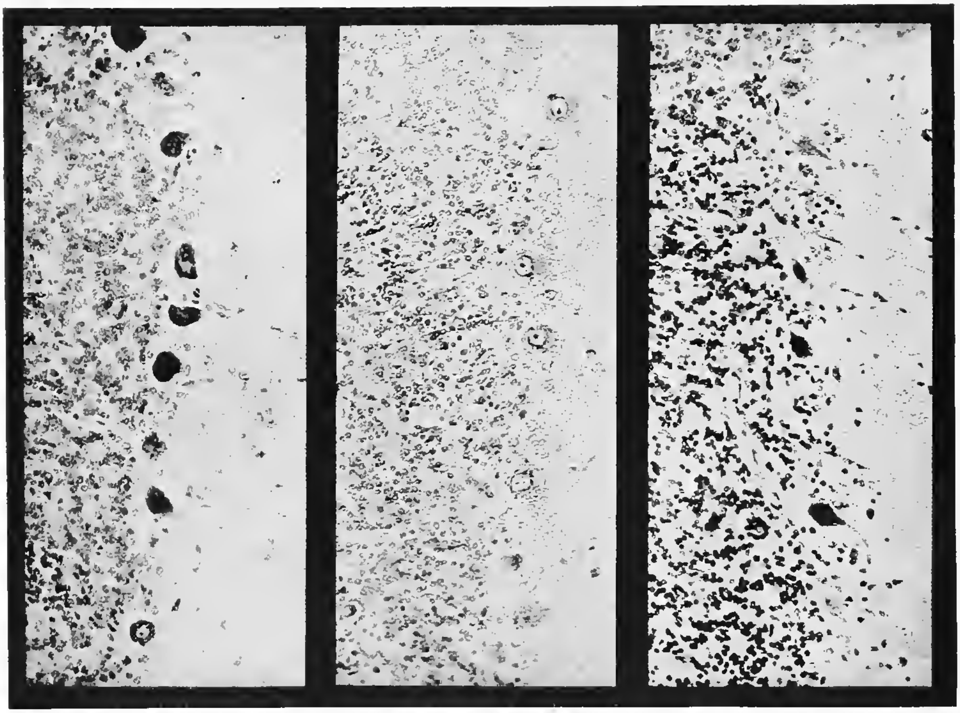
FIG. 59.—Comparative Effects of Diphtheria Toxin and of Diphtheria Toxin plus Morphin on the Brain-Cells, Livers, and Adrenals of Rabbits.

A, Section of normal cerebellum.
B, Section of cerebellum after administration of diphtheria toxin.
C, Section of cerebellum after administration of diphtheria toxin plus morphin.
D, Section of normal liver.
E, Section of liver after administration of diphtheria toxin.
F, Section of liver after administration of diphtheria toxin plus morphin.
G, Section of normal adrenal.
H, Section of adrenal after administration of diphtheria toxin.
I, Section of adrenal after administration of diphtheria toxin plus morphin.

(A to C from photomicrographs, × 310.) (D to I from photomicrographs, × 1640.)

these phenomena is that they are due only to the want of oxygen, then why is not the activity of the respiratory system diminished also for the same reason ?

In our experiments we found that asphyxia produced brain, liver, and adrenal changes of the same type as those produced by trauma, by emotion,



A B C

FIG. 60.—Comparative Effects of Ether and of Nitrous Oxid on the Brain-Cells of Dogs.

A, Section of normal cerebellum of dog (× 310). B, Section of cerebellum of dog after the continuous administration of ether for four hours (× 310). C, Section of cerebellum of dog after the continuous administration of nitrous oxid for four hours (× 310).

Compare the hypochromatic and disorganised appearance of the Purkinje cells in B with the hyperchromatic Purkinje cells in C.

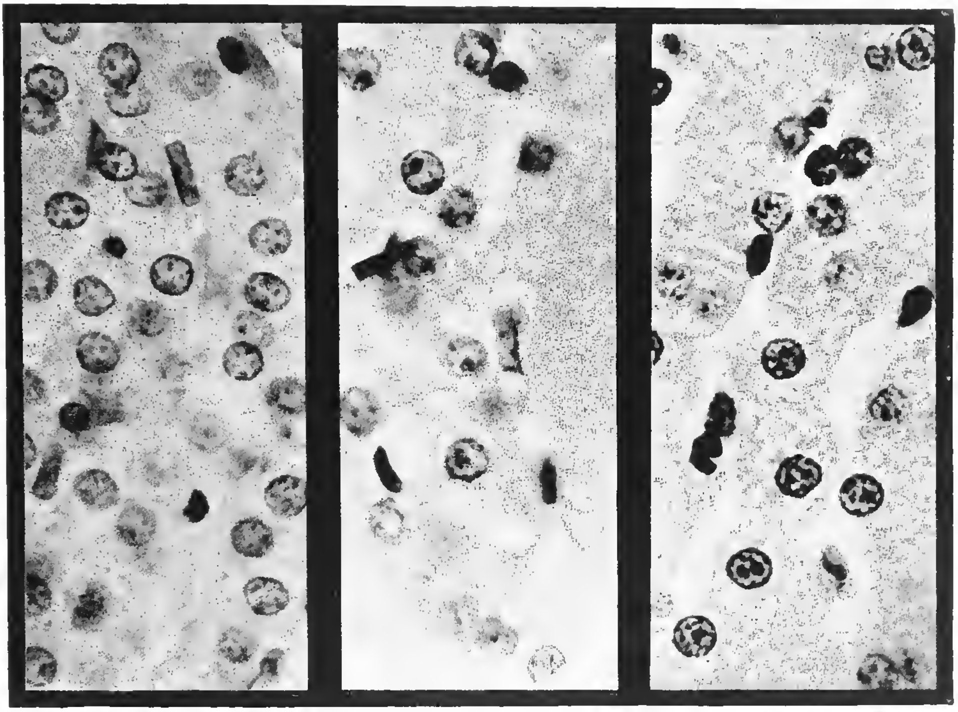
by exertion, by insomnia. We found also that, like the other causes of exhaustion, asphyxia caused an increased output of adrenalin, and acidosis of the blood. Thus, like results were produced in the one case by want of oxygen, in the other by excessive oxidation.

In aviation and mountain climbing at a height where the oxygen is rarefied, in poisoning by phosgene gas, in any case in which there is diminished rather

than excessive oxidation, the oxidation balance may be disturbed and exhaustion established.

ANESTHETICS

The exhaustion following chloroform and ether anesthesia suggested a research to determine whether or not these anesthetics caused demonstrable



A B C

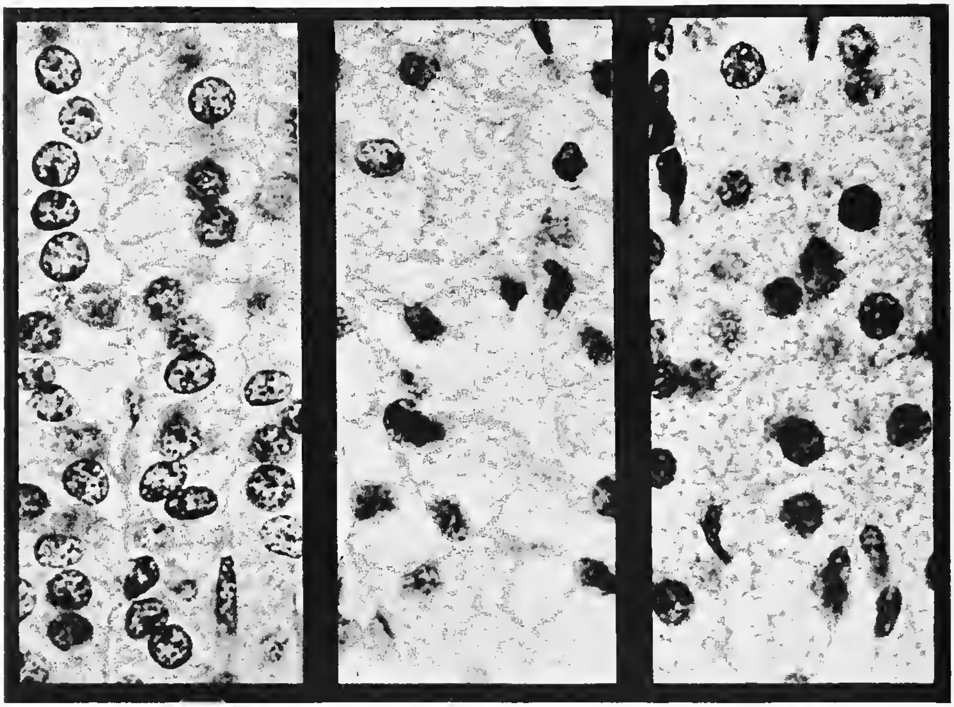
FIG. 61.—Comparative Effects of Ether and of Nitrous Oxid on the Livers of Dogs.

A, Section of the normal liver of a dog (× 1640). B, Section of liver of a dog after the continuous administration of ether for four hours (× 1640). C, Section of liver of a dog after the continuous administration of nitrous oxid for four hours (× 1640).

Although the conservative effect of nitrous oxid is not as evident in the liver as in the adrenals or the cerebellum, yet here also the disappearance of cell substance and of nuclei is much more marked in B than in C.

lesions, or whether the resultant exhaustion was due merely to the retention of the anesthetic substance in the organism. We therefore subjected dogs and rabbits to prolonged ether, chloroform, chloretone, and nitrous oxid anesthesia. In collaboration with Dr. Menten, we found that these inhalation

anesthetics caused acute blood acidosis; that after four hours continuous ether, chloroform, or chloretone anesthesia, marked histologic changes appeared in the brain, the liver, and the adrenals; that animals subjected to from four to six hours of continuous ether anesthesia might die on the following day;



A B C

FIG. 62.—Comparative Effects of Ether and of Nitrous Oxid on the Adrenals of Dogs.

A, Section of normal adrenal of dog (× 1640).

B, Section of adrenal of dog after continuous administration of ether for four hours (× 1640).

C, Section of adrenal of dog after continuous administration of nitrous oxid for four hours (× 1640).

Note the disappearance of cytoplasm and of some nuclei and the irregular shapes of other nuclei in B as compared with the general conservation of cytoplasm and the well-shaped abundant nuclei in C.

that the lesions produced by an equal continuous period of nitrous oxid anesthesia were negligible as far as the brain was concerned, though certain changes appeared in the liver (Figs. 60-62). The contrast between the brain-cell changes produced by ether and those produced by nitrous oxid was striking.

ELECTRIC STIMULATION

What is the cause of the suspension of function which is sometimes seen as a result of heavy electric shocks in accidents to workers in electric light

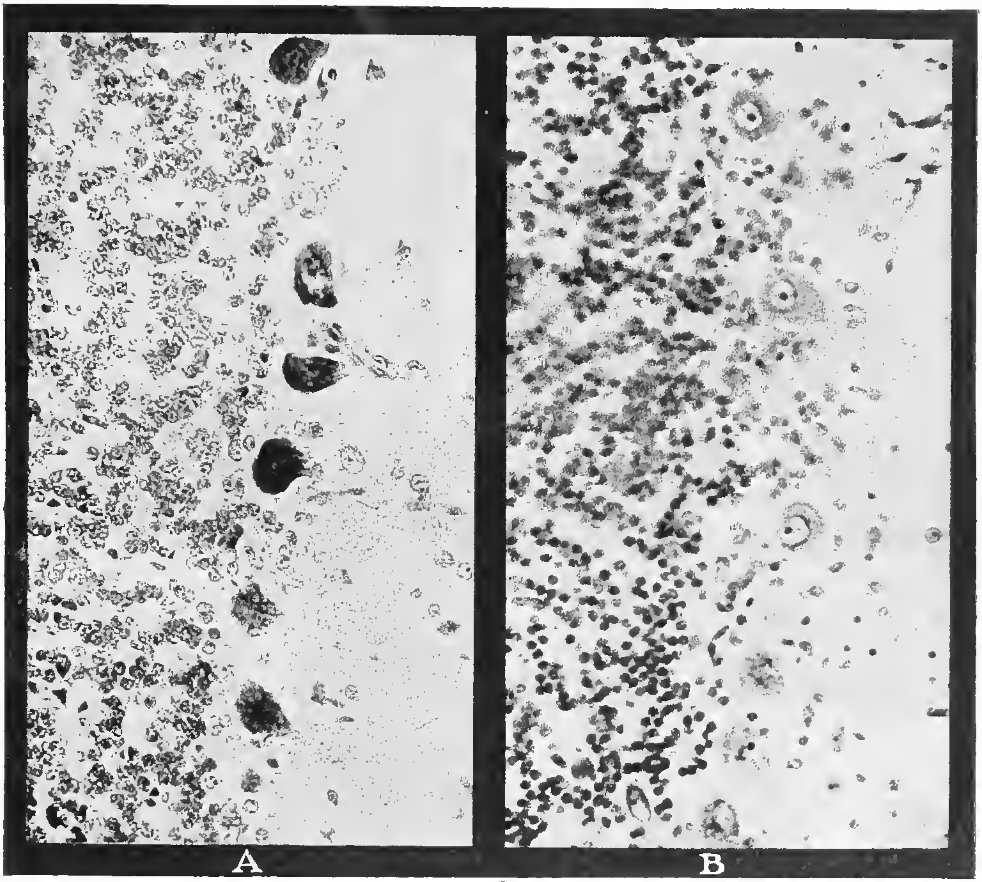
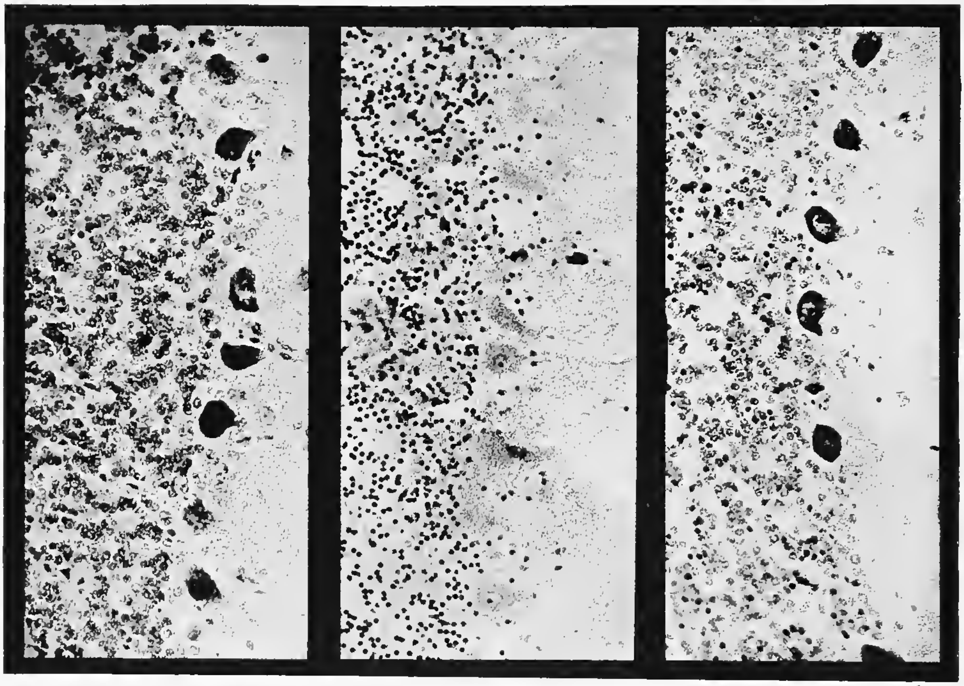


FIG 63.—Effect of Electric Stimulation of the Spinal Cord on the Cerebellum of a Dog.
A, Section of normal cerebellum of dog. B, Section of cerebellum of dog after electric stimulation of the spinal cord.

Compare the disintegrating Purkinje cells in B with the intact cells in A. (From photomicrographs, × 310.)

plants, or in the impaired vision which results from excessive stimulation of the optic nerve, as by a flash of lightning? Does excessive electric stimulation, like excessive traumatic, excessive emotional, or excessive toxic stimulation, overwhelm the nerve-cells and cause comparable histologic changes?

Experiments showed that prolonged electric stimulation of the nerve supply of organs caused an increase in function ; that excessive electric stimulation caused a suspension of function ; that sufficiently intense stimulation, as in electrocution, produced disruptive effects in the central nervous system ;



A B C

FIG. 64.—The Protective Effect on the Brain-Cells of a Dog of Injections of an Alkali after Double Adrenalectomy.

A, Section of normal cerebellum of a dog (× 310). B, Section of cerebellum of a dog after double adrenalectomy (× 310). C, Section of cerebellum of a dog after double adrenalectomy followed by injections of sodium bicarbonate (× 310).

Note the disintegration and disappearance of Purkinje cells in B, and the normal intact condition of the Purkinje cells in C. This and the following figure demonstrate the neutralising function of the adrenals.

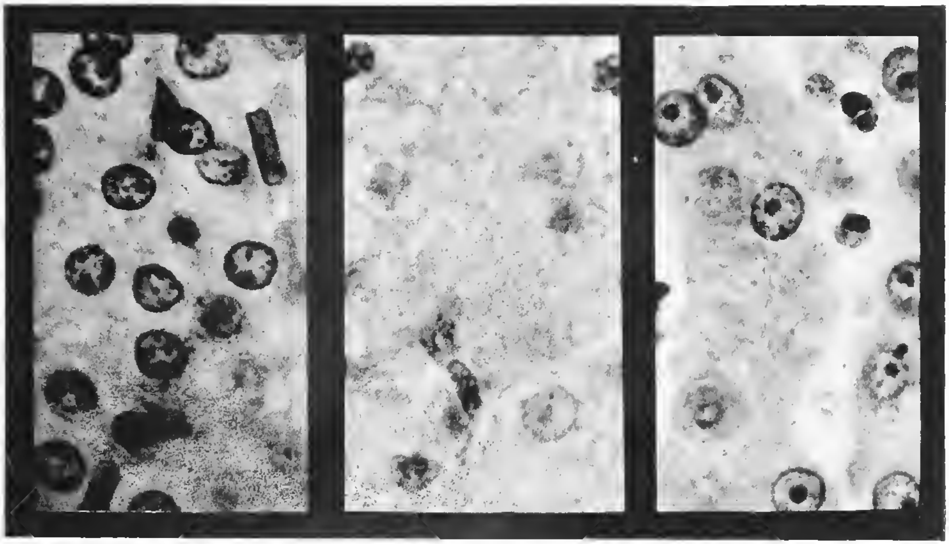
that prolonged electric stimulation of the spinal cord or of the cortex of the brain caused brain-cell changes of the same type as the changes seen in exhaustion from other causes (Fig. 63).

Electricity, like trauma, like emotion, like toxins, within a certain range, may stimulate and cause physiologic fatigue ; or, in excess, it may overwhelm

the brain-cells and interfere with their function. That is, electric stimulation may cause *exhaustion* ; it may cause *shock*.

EXCISION OF ORGANS

In order that some light might be thrown upon the relations of certain organs to the brain, a series of experiments was performed to determine the effect of their excision.



A B C

Fig. 65.—The Protective Effect on the Liver of a Dog of Injections of an Alkali after Double Adrenalectomy.

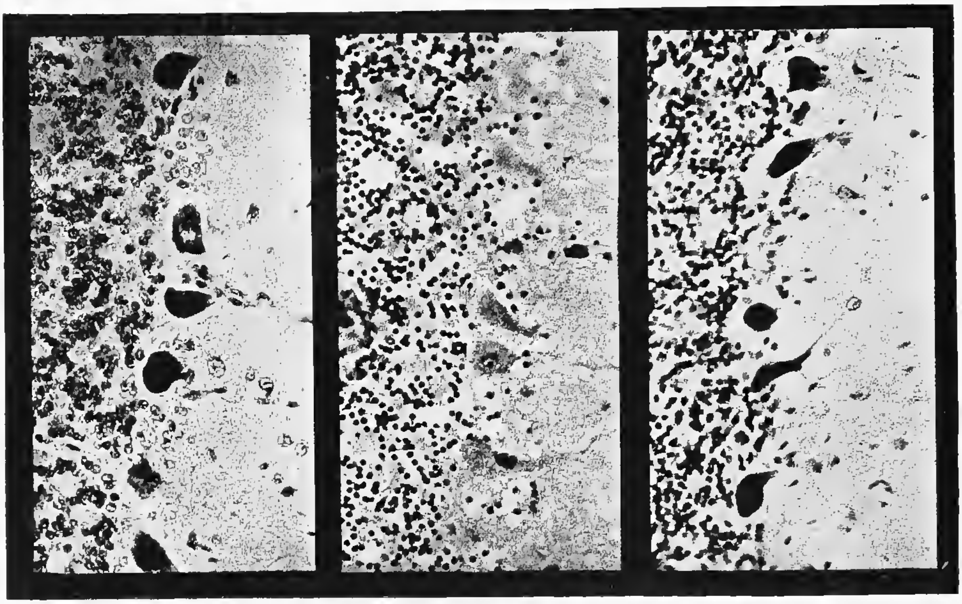
A, Section of normal liver of a dog (× 1640). B, Section of liver of a dog after double adrenalectomy (× 1640). C, Section of liver of a dog after double adrenalectomy followed by injections of sodium bicarbonate (× 1640).

Note the disappearance of cytoplasm and of nuclei from B as compared with the normal and numerous nuclei and the conserved cytoplasm in C.

Excision of the adrenals and the injection of adrenalin.—Excision of the adrenals is known to be followed by a progressive fall in the body temperature and progressive exhaustion until death. Histologic examination showed no stage of hyperchromatism after adrenalectomy, but a progressive chromatolysis of the brain-cells and of the cells of the liver.

If, after the adrenals were removed, the animal was subjected to one of the causes of hyperchromatism in a normal animal, such as strychnin, physical

injury, foreign protein, etc., *no hyperchromatic stage* appeared; on the contrary, nothing seemed to alter the course of the progressive cytolysis of the brain-cells. Adrenalectomised animals succumbed far more readily to traumatic shock than normal animals. Adrenalectomised animals were more depressed by ether, and made a slower recovery from ether anesthesia than normal animals.



A B C

FIG. 66.—Comparative Effects of Excision of the Adrenal Glands and of Excessive Administration of Adrenalin on the Brain-Cells of Dogs.

A, Section of normal cerebellum of a dog (× 310). B, Section of cerebellum of dog after adrenalectomy (× 310). C, Section of cerebellum of dog after repeated injections of adrenalin (× 310).

The disastrous effects of withdrawing adrenalin from the kinetic system is apparent in B in the extensive loss of chromatic material in all the cells, the cellular disintegration of many and the almost complete degeneration of some cells. The effect of a continuous activation of the system by the excessive administration of adrenalin is strikingly shown in C by the large number of hyperchromatic cells, together with the evidences of exhaustion and disintegration in some cells. These effects are similar in kind, and analogous to the effects produced by withdrawing thyroid secretion or by administering excessive doses of thyroid extract.

In adrenalectomised animals, blood acidosis did not appear until just before death. After adrenalectomy, death was somewhat, but not strikingly delayed by the administration of large amounts of sodium bicarbonate (Figs. 64 and 65). Sodium bicarbonate prevented the development of acute ulcer of the stomach which occurs after double adrenalectomy.

In another series of experiments we administered excessive doses of adrena-

lin intravenously, subcutaneously, in the gall-bladder, in the peritoneum. It was given by itself alone and with oil, in single and in repeated doses. We found that adrenalin causes an immediate rise in temperature ; that it causes an immediate leucocytosis (Mosiman); that it causes first a marked hyperchromatism of the brain-cells, followed by a later chromatolysis (Fig. 66);

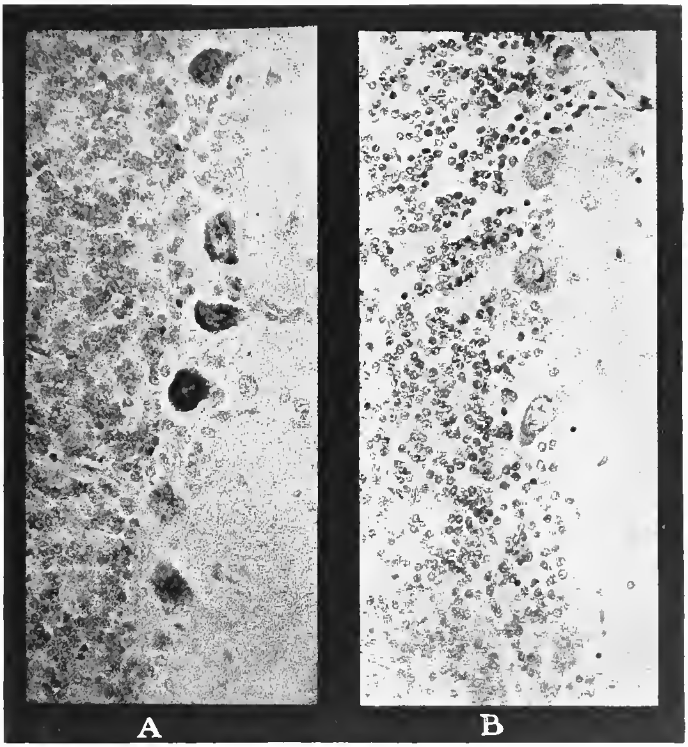


Fig. 67.—Effect of Hepatectomy upon the Cerebellum.

A, Normal cerebellum.
B, Cerebellum of animal upon which hepatectomy has been performed.

(From photomicrographs, × 310.)

that it causes changes in the cells of the liver similar to those in the brain-cells—first, a markedly increased stainability, followed by edema and chromatolysis. Repeated excessive doses of adrenalin on successive days caused emaciation, exhaustion, and changes typical of exhaustion in the cells of the brain and the liver.

Excision of the Liver.—Excision of the liver was followed by a rapid decline in muscular power and in heat production until death, which in most

instances occurred within a few hours. Histologic studies showed extreme chromatolysis of the brain-cells and disintegration of the cells of the adrenals (Fig. 67). Just before death, the H-ion concentration of the blood increased rapidly.

Thyroidectomy and Excessive Thyroid Feeding—Iodism.—Animals in myxedema showed brain-cell changes typical of exhaustion (Fig. 68), and

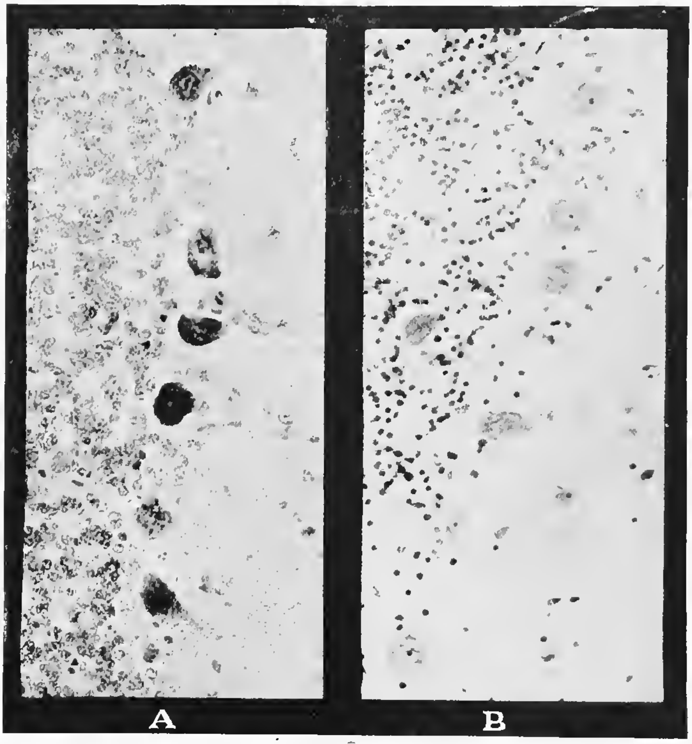


Fig. 68.—Effect of Thyroidectomy upon the Cerebellum.

A, Normal cerebellum.
B, Cerebellum of animal upon which thyroidectomy had been performed.

(From photomicrographs, × 310.)

excessive thyroid feeding also caused exhaustion and similar cytologic changes. Examination of the brains of cases which had died of exophthalmic goiter showed a similar picture (Fig. 69). Acute iodism induced by the injection of iodoform into the peritoneal cavity produced a like sequence of clinical symptoms and histologic changes (Figs. 70-72).

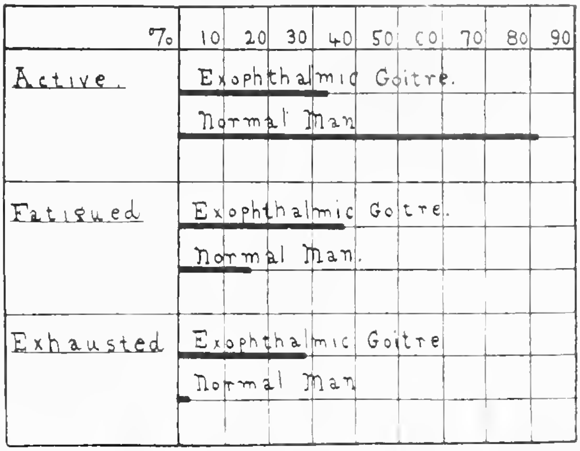
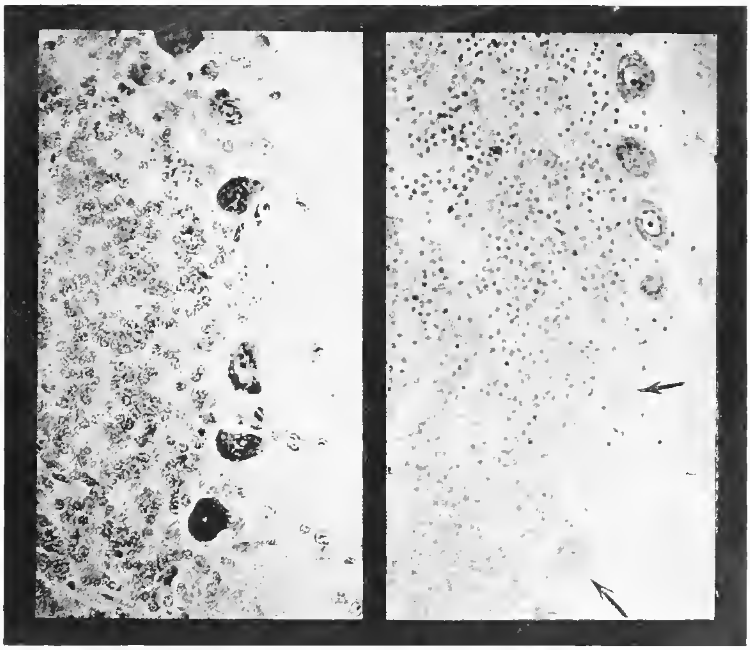


FIG. 69.—Differential Purkinje Cell Counts. Exophthalmic Goiter. The chart represents the average derived from five clinical cases.



A B

FIG. 70.—Effect of Iodoform on the Brain-Cells of a Dog.

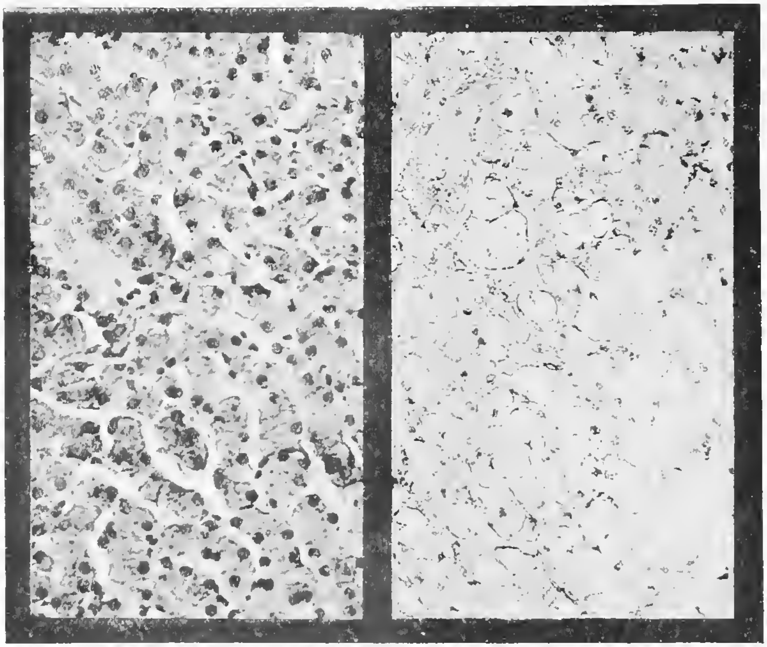
A, Section of normal cerebellum of dog (× 310).

B, Section of cerebellum of dog after repeated injections of iodoform (× 310).

Note the general disappearance of chromatic material from the cells of B, as compared with the deeply stained, intact cells of A.

COMPARISON OF THE EFFECTS OF EXHAUSTION IN VARIOUS SPECIES OF ANIMALS

Most of the investigations summarised above were made with dogs and rabbits, but certain corresponding studies were made in a wide range of species. We applied shock or exhaustion-producing stimuli to birds, to reptiles, to



A B

Fig. 71.—Effect of Iodoform on the Liver of a Dog.

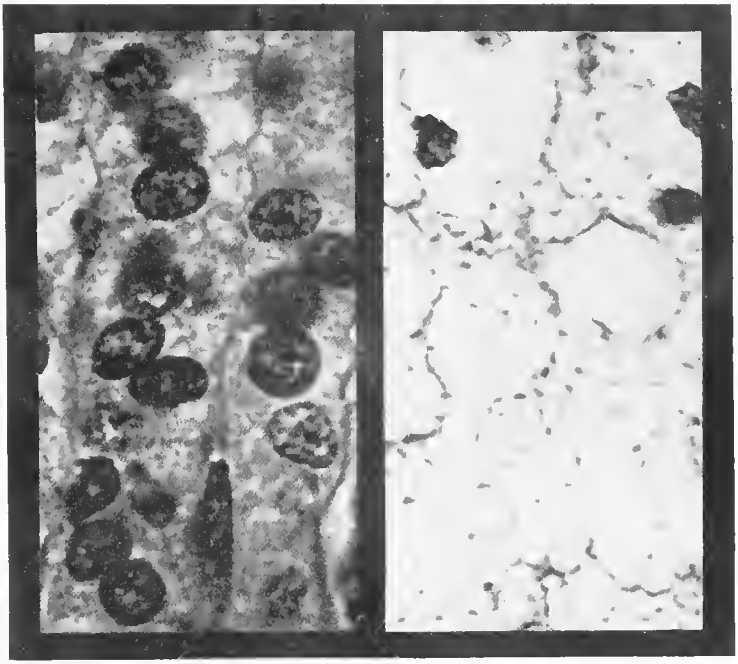
A, Section of normal liver of dog (× 310). B, Section of liver of dog after repeated injections of iodoform (× 310).

Note the extensive vacuolated areas and the disappearance of nuclei in B.

porcupines, to armadillos, to skunks, and, as we have described in another section, to salmon and to electric fish. We found in every instance the same cycle of changes—the same histologic evidence of exhaustion, *provided and always provided* that the animal lived for two or more hours in shock or exhaustion before the specimens were secured. One especially valuable set of observations was made of hibernating woodchucks which had been wakened and immediately frightened by dogs. The brain-cells of the hibernating animals were the most perfect we found in any animal—a significant observa-

tion in view of other evidences of the protective and restorative power of sleep. The brain-cells of the woodchucks subjected to fear showed the typical cycle of exhaustion (Figs. 73-76).

Finally, to all these laboratory data we added studies of human material in exhaustion from disease, from injury, and from the various stimuli of war (Figs. 77-82).



A B

FIG. 72.—Effect of Iodoform on the Adrenals of a Dog.

A, Section of normal adrenal of dog (× 1640). B, Section of adrenal of dog after repeated injections of iodoform (× 1640).

Note the widespread loss of cytoplasm and the vacuolisation of some cells in B.

VII. Exhaustion and Shock-Producing Effects of Various Agents as Evidenced by Changes in H-ion Concentration and in Reserve Alkalinity

H-ION CONCENTRATION

Experiments in collaboration with Dr. M. L. Menten[1] showed that the H-ion concentration of the blood was increased in every type of intense,

[1] Menten, M. L., and Crile, G. W.: *Am. J. Physiol.*, 1915, xxxviii, 225-232.

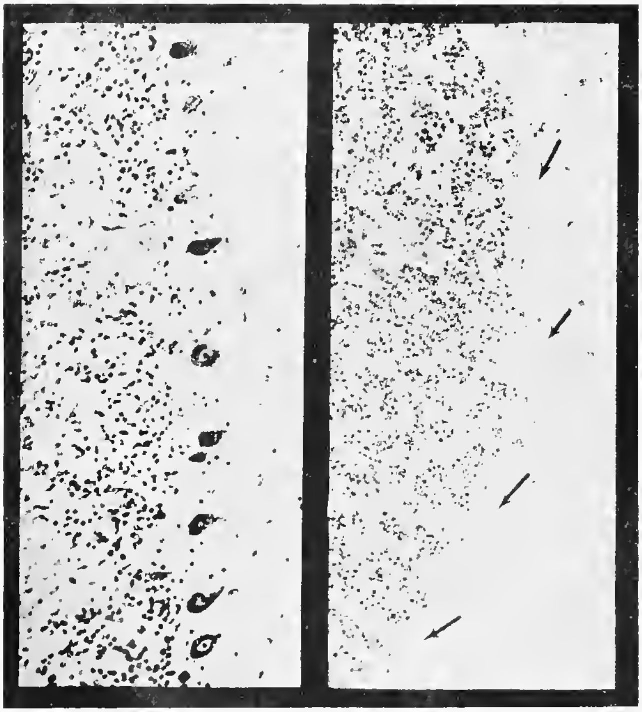
A  B

FIG. 73.—Effect of Repeated Fright on the Cerebellum of a Woodchuck.

A, Section of cerebellum of hibernating woodchuck (310).

B, Section of cerebellum of woodchuck showing effect of extreme emotion (fright) (310).

Note the almost complete disappearance of Purkinje cells in B. (See arrows.)

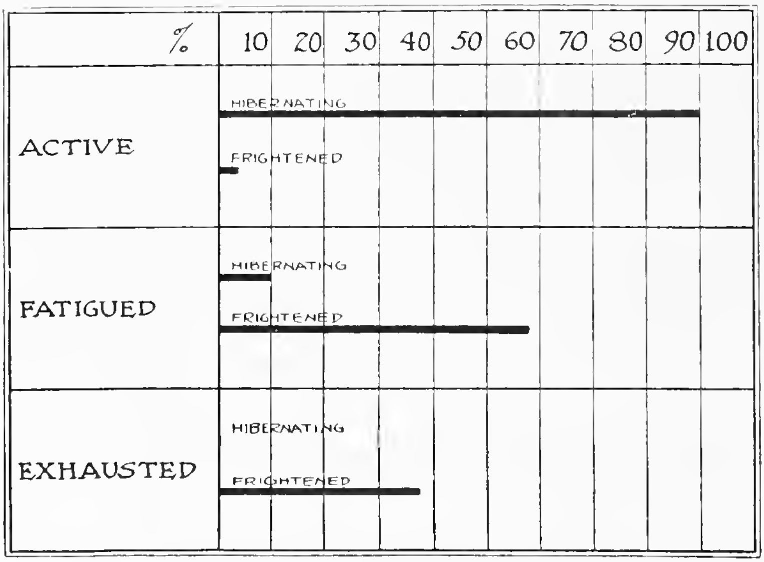


FIG. 74.—Comparison of the Differential Purkinje Cell Counts in Hibernating and in Frightened Woodchucks.

overwhelming activation—by intense exertion, by intense emotion, by intense trauma; it was increased also by inhalation anesthesia, by hemorrhage, by asphyxia, several hours after excision of the liver, near the death-point after

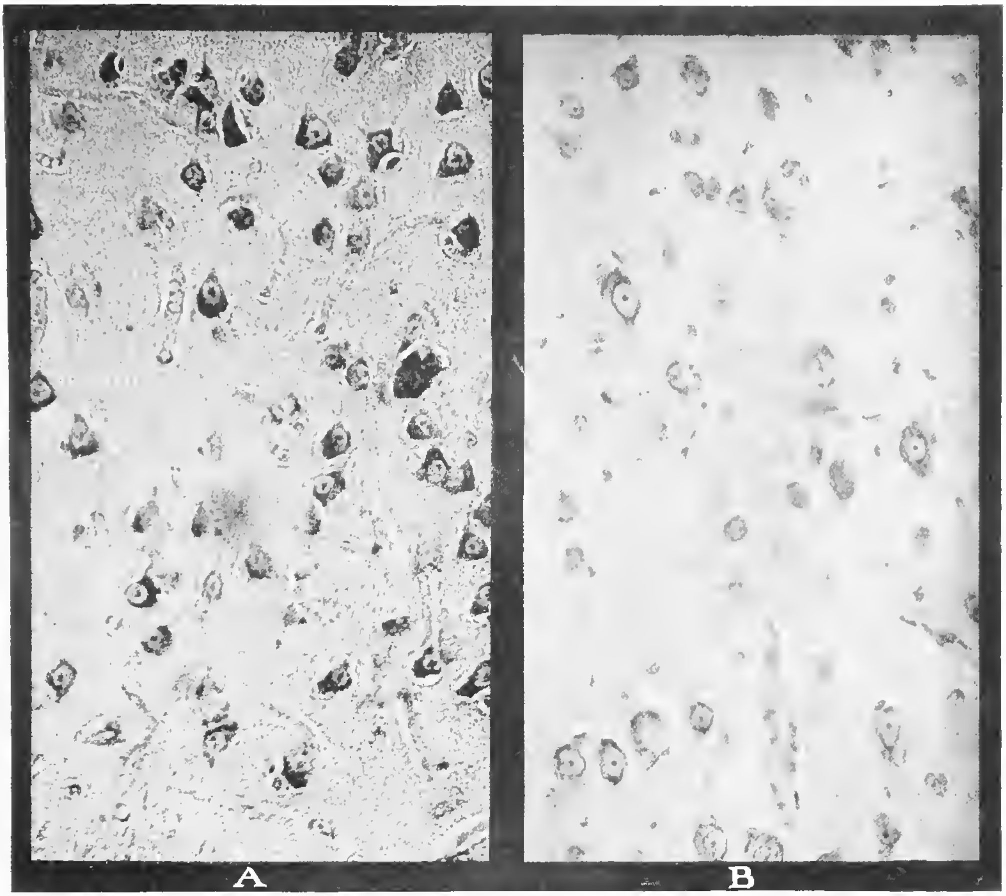


Fig. 75.—Late Effects of Fear on the Cerebrum of a Woodchuck.

A, Section of cerebrum of hibernating woodchuck.
B, Section of cerebrum of a woodchuck killed four hours after one seance of fright.

(From photomicrographs, 310.)

excision of the adrenals, and near the point of dissolution, whatever the cause of death. The H-ion concentration was not increased during sleep, during narcosis by opium or its derivatives, during prolonged insomnia, nor until near the death-point after decapitation in animals in which artificial respiration was maintained. In the clinic we found that the H-ion concentration

was not increased in many instances of serious, even fatal disease, such as infection, exophthalmic goiter, cardio-vascular disease, typhoid fever. The clinical application of these findings was disappointing.

RESERVE ALKALINITY AND ACID EXCRETION IN THE URINE

In collaboration with Drs. Crozier, Rogers and Harrison [1] numerous observations on the reserve alkalinity of the blood were made by the Van Slyke

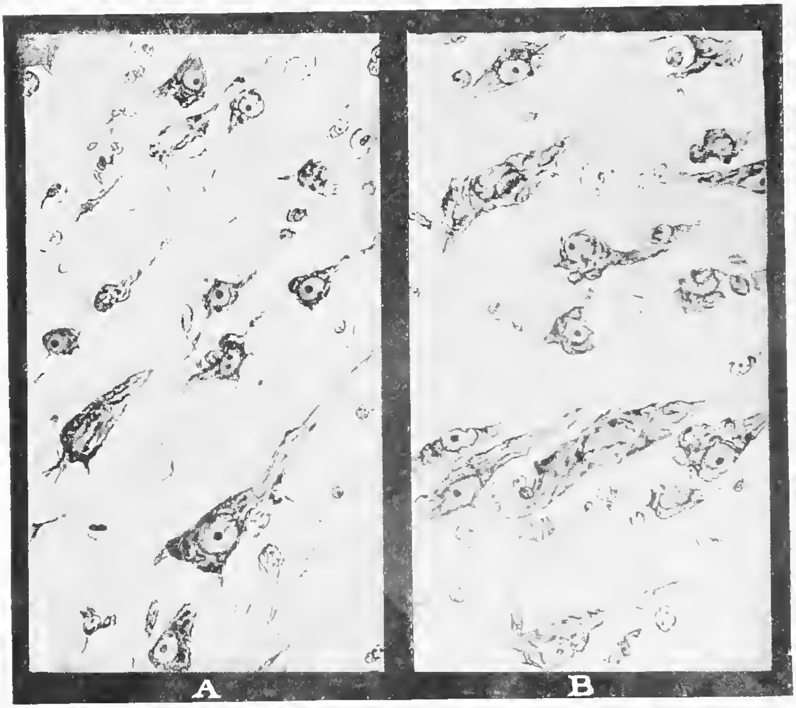
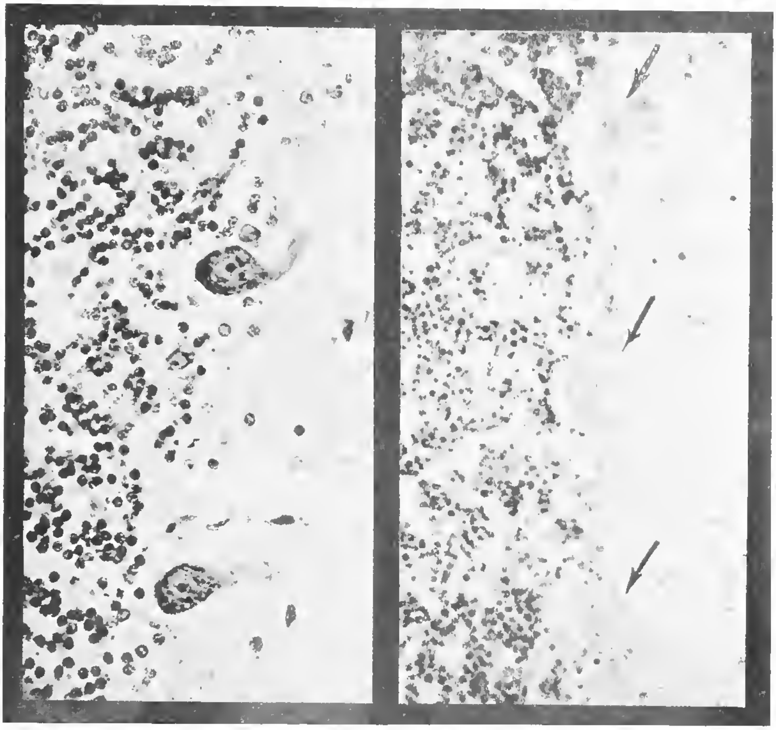


Fig. 76.—Effect of One Seance of Fright on the Medulla of a Woodchuck.
A, Section of medulla of a hibernating woodchuck.
B, Section of medulla of a frightened woodchuck.
Note the generally disorganised appearance of the cells in B.
(From camera lucida drawings.)

method, and on the acid excretion of the urine by the method of L. J. Henderson. We found varying degrees of reduction in reserve alkalinity and alterations in the acid excretion in the urine in animals in shock, under inhalation anesthesia, in infection, in asphyxia, in strychnin poisoning, in

[1] Crozier, W. H., Rogers, W. B., and Harrison, B. I.: *Surg. Gyn. Obst.*, 1915, xxi. 722-727.

hemorrhage, in iodoform poisoning, in exertion, in emotion. As in our measurements of the H-ion concentration in the clinic, we found that the reserve alkalinity was not reduced, nor the acid excretion in the urine altered, in many cases of acute infections, in exophthalmic goiter, in good or in bad risks of any kind.



A B

Fig. 77.—Effect of Infection (Streptococcal) on the Brain-Cells of a Human Being.

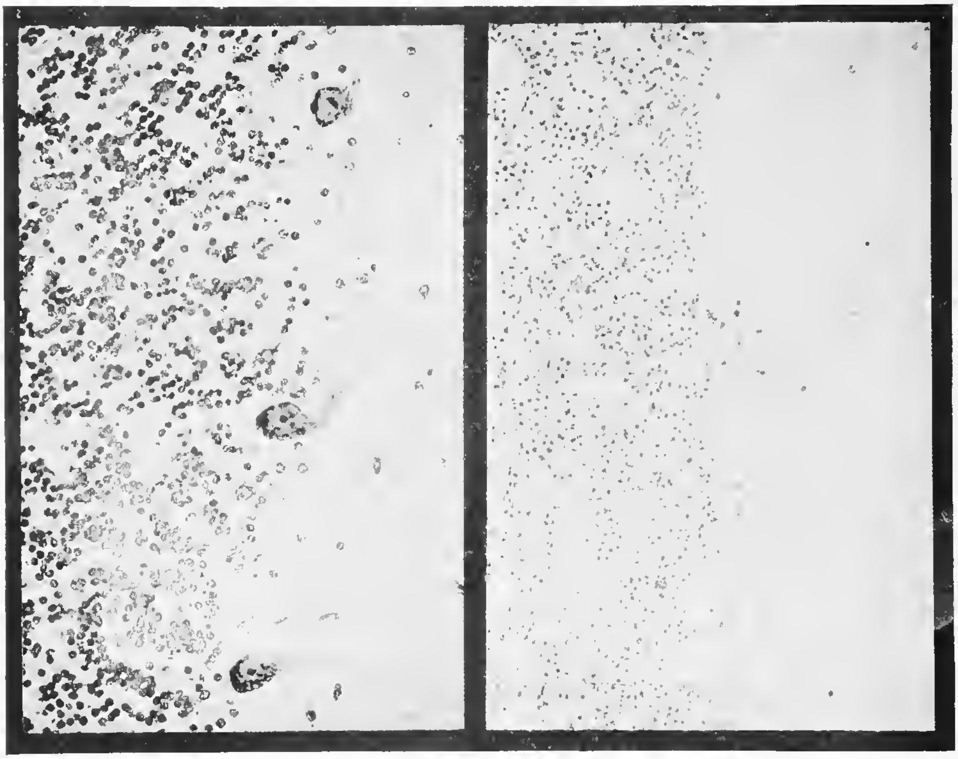
A, Section of normal human cerebellum (× 310). B, Section of human cerebellum after death from infection (× 310).

Note the marked disintegration of the Purkinje cells in B.

In the laboratory of U.S. Base Hospital No. 4 (The Lakeside Unit) in France, Major A. N. Eisenbrey and Lieutenant F. De Eds made comparative studies of the blood from the longitudinal sinus and from the femoral vein, by Martin's titration method, to determine the presence of changes in metabolism as a primary result of massive injury. They found that under nitrous oxid anesthesia the alkaline reserve was higher in the blood from the femoral vein than in the blood from the longitudinal sinus. With but one exception, the

blood taken after a half-hour of trauma showed a higher alkaline reserve in both the longitudinal sinus and the femoral vein, *i.e.* comparing sinus with sinus and vein with vein (Fig. 83).

The question arises as to whether or not the increased alkaline reserve is only apparent and is due to increased concentration of the blood during shock.



A B

Fig. 78.—Effect of Acidosis on the Brain-Cells of a Human Being.

A, Section of normal human cerebellum (× 310).

B, Section of human cerebellum showing the effect of acidosis (× 310). There are no active cells present, but faint traces of the Purkinje cells are visible.

These results indicate that in shock the brain suffers an immediate impairment, the diminished brain-cell activity being reflected in the reserve alkalinity of the blood coming from the brain. Certain deductions from these findings will be made in a later chapter.

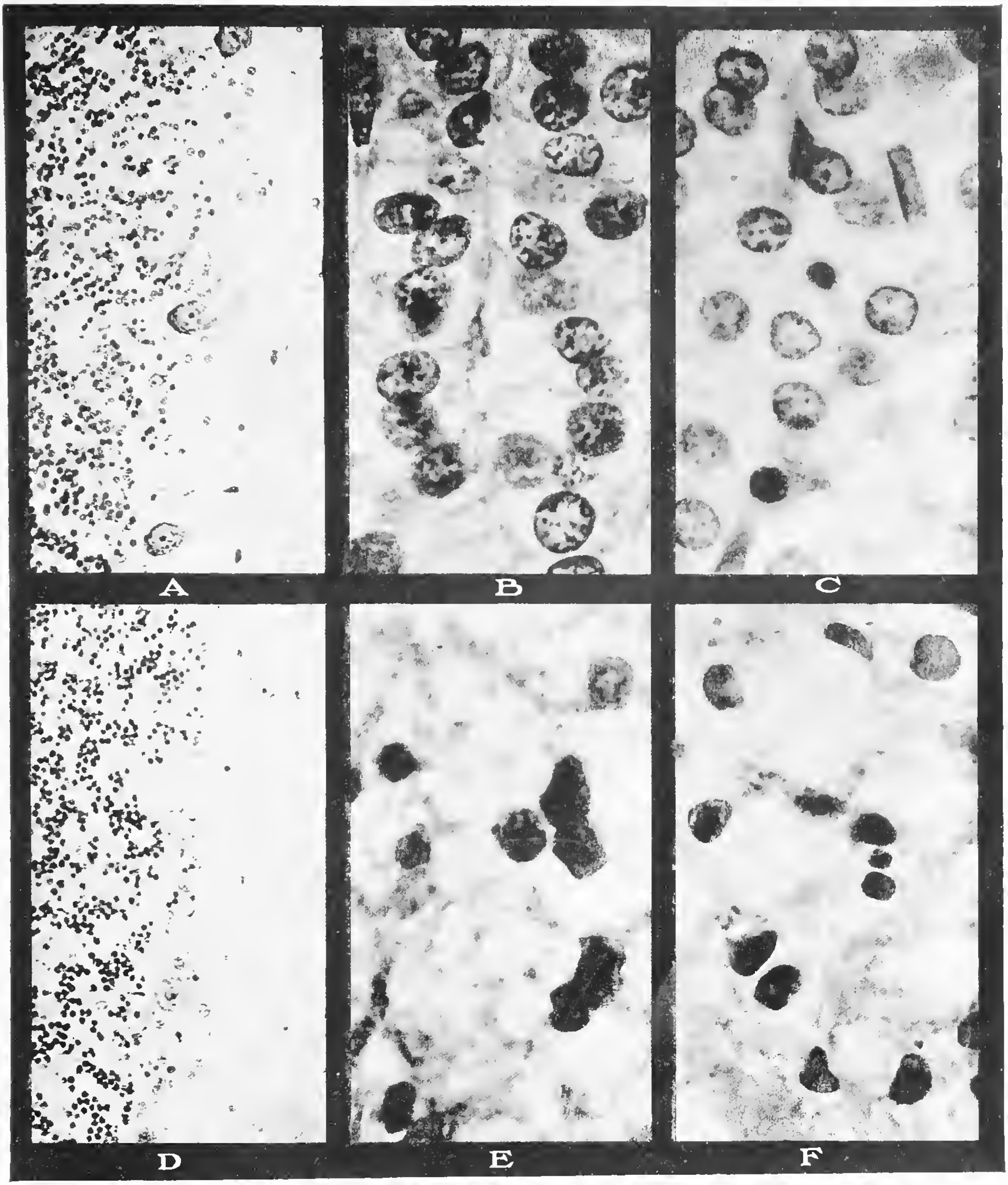


FIG. 79.—Effect of Combined Stimuli, chief among which were Insomnia, Exertion, and Emotion, on the Brain, Adrenals, and Liver of a Soldier. (Case I.)

A, Section of normal cerebellum.
B, Section of normal adrenal.
C, Section of normal liver.
D, Section of cerebellum of soldier.
E, Section of adrenal of soldier.
F, Section of liver of soldier.

(A and D from photomicrographs, × 310.) (B, C, E, and F from photomicrographs, × 1640.)

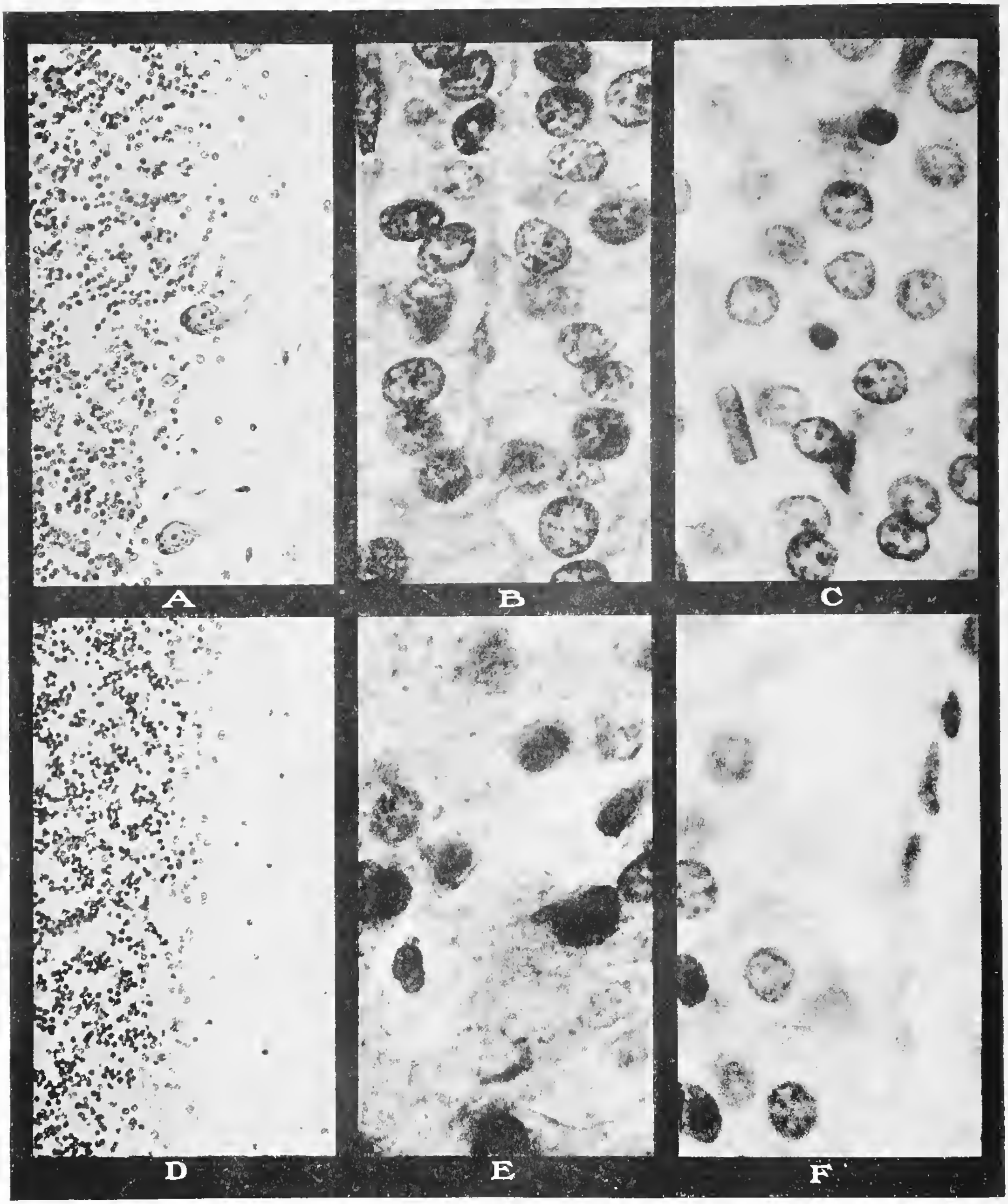


FIG. 80. Effect of Combined Stimuli, chief among which were Insomnia, Exertion, and Emotion, on the Brain, Adrenals, and Liver of a Soldier. (Case II.)

A, Section of normal cerebellum.
B, Section of normal adrenal.
C, Section of normal liver.

D, Section of cerebellum of soldier.
E, Section of adrenal of soldier.
F, Section of liver of soldier.

(A and D from photomicrographs, × 310.) (B, C, E, and F from photomicrographs, × 1640.)

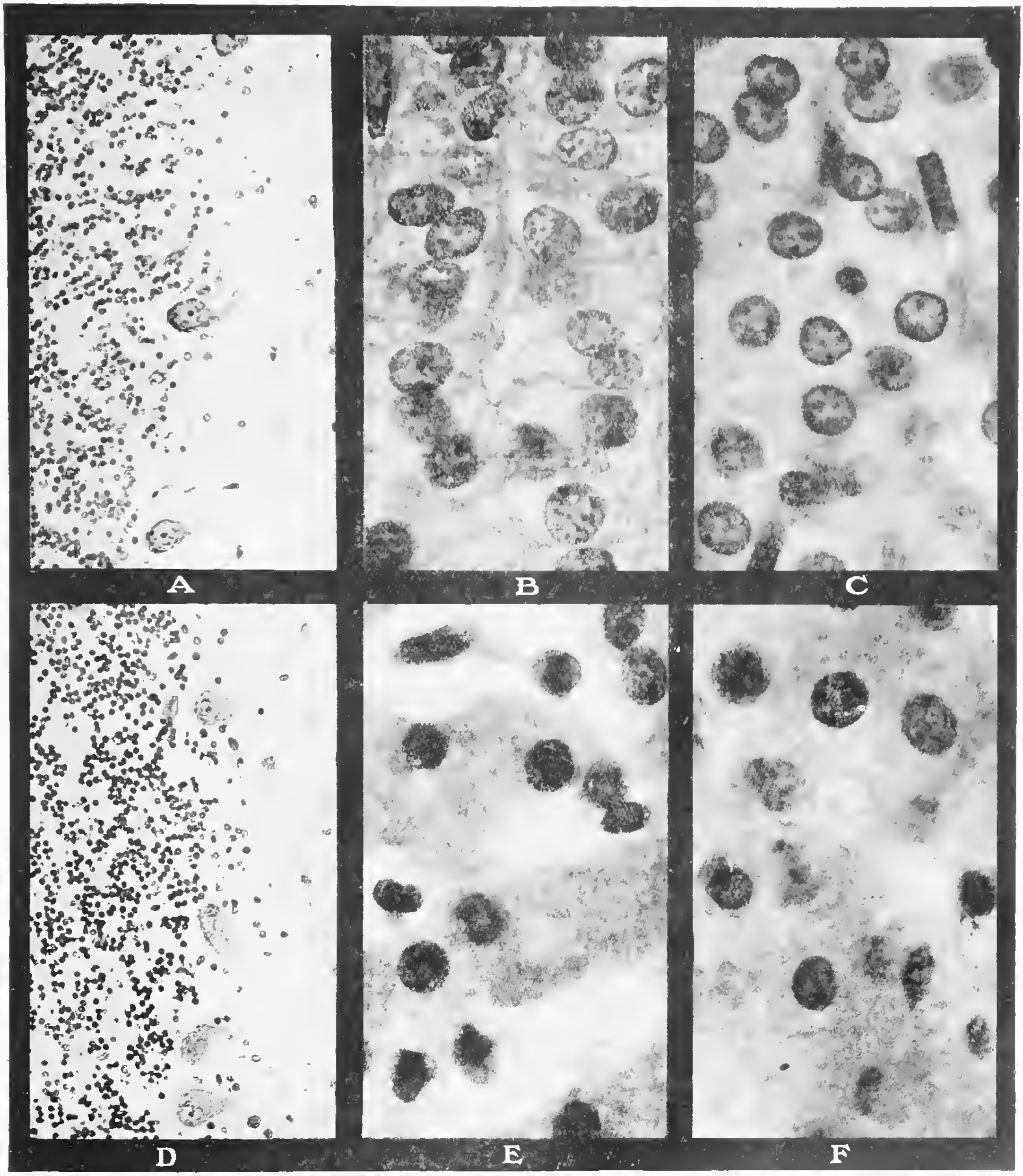


FIG. 81.—Effect of Combined Stimuli, chief among which were Insomnia, Exertion, and Emotion, on the Brain, Adrenals, and Liver of a Soldier. (Case III.)

A, Section of normal cerebellum. D, Section of cerebellum of soldier.
B, Section of normal adrenal. E, Section of adrenal of soldier.
C, Section of normal liver. F, Section of liver of soldier.

(A and D from photomicrographs, × 310.) (B, C, E, and F from photomicrographs, × 1640.)

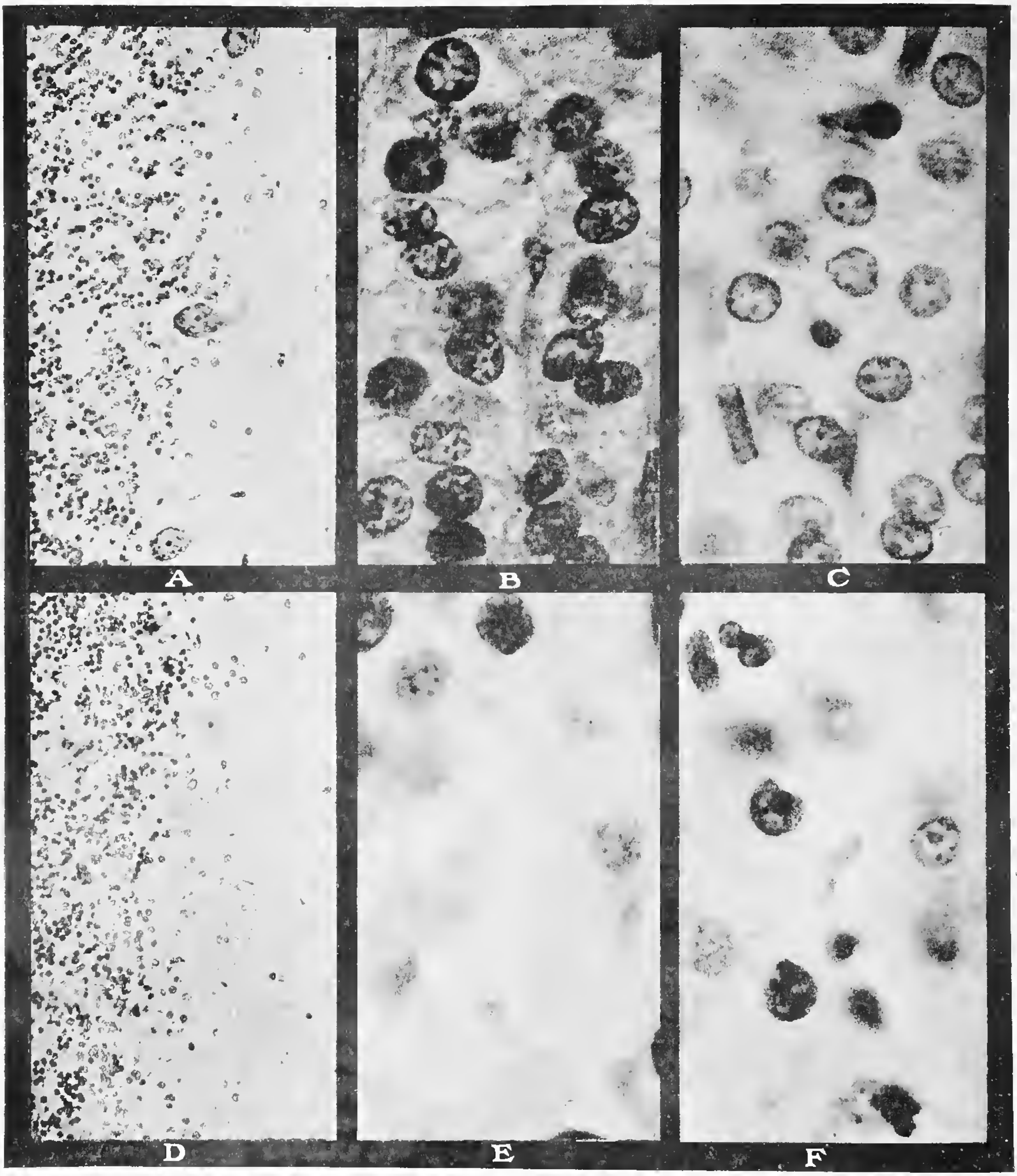


FIG. 82.—Effect of Combined Stimuli, chief among which were Insomnia, Exertion, and Emotion, on the Brain, Adrenals, and Liver of a Soldier. (Case IV.)

A, Section of normal cerebellum.
B, Section of normal adrenal.
C, Section of normal liver.
D, Section of cerebellum of soldier.
E, Section of adrenal of soldier.
F, Section of liver of soldier.

(A and D from photomicrographs, 310.) (B, C, E, and F from photomicrographs, 1640.)

VIII. Exhaustion and Shock-Producing Effects of Various Agents as Evidenced by Changes in the Electric Conductivity of Certain Tissues

The histologic changes in exhaustion, notably those in the brain and in the liver, led us to expect an alteration in the electrolytic content and consequently in the conductivity of the cells. The first point was in part determined by the preliminary observations of Major Eisenbrey and Lieutenant De Eds, which were described in the preceding section. A research to determine the second point was initiated in collaboration with Capt. G. B. Obear, and has been continued in collaboration with Miss Helen R. Hosmer and Miss Amy F. Rowland. This research was suggested by the studies of the permeability of living cells which have been made by Osterhout, Galeotti, Lillie, Loeb, and others.

This research is now in progress. Thus far we have measured the conductivity of 4798 sections of various tissues from 436 rabbits and 137 clinical

FIG. 83.—Comparative Percentile Increase in Reserve Alkalinity in the Inceptive Stage of Surgical Shock.

specimens. The tissues have included the cerebrum, the cerebellum, and the liver of every rabbit studied; and in many of them also the spinal fluid, the blood, the adrenals, the thyroid, the spleen, the pancreas, the kidneys, and the voluntary and involuntary (heart) muscle.

After establishing the apparent range of conductivity of these tissues, especially the brain and the liver, in normal animals, under varying conditions —varying lengths of confinement, different seasons, etc., groups of rabbits were subjected to exhaustion from various causes—prolonged insomnia, extreme fright, physical trauma (surgical shock), infection, hydrochloric acid injection, thyroid feeding, iodoform poisoning, strychnin poisoning, prolonged ether anesthesia, prolonged nitrous oxid anesthesia. We have observed also the effect upon the electric conductivity of the brain and the liver of the inceptive stage of surgical shock, of toxic shock, of strychnin and adrenalin shock. We have observed also the effects of sleep and of rest after prolonged insomnia, and of morphin in the presence of infection. We have measured the conductivity of the brain and of the liver in fetuses, in new-born and in young rabbits.

The pathological tissues measured have included exophthalmic goiters, adenomata, colloid goiters, malignant thyroids, X-ray burns, uterine fibroids, breast cysts, and various types of carcinomata and sarcomata.

Our general findings may be summarised as follows :—

(1) The normal conductivity for each of the tissues studied can be estimated within a narrow range—from one to six per cent., while the changes typical of exhaustion have varied from two to ninety-six per cent. The con-

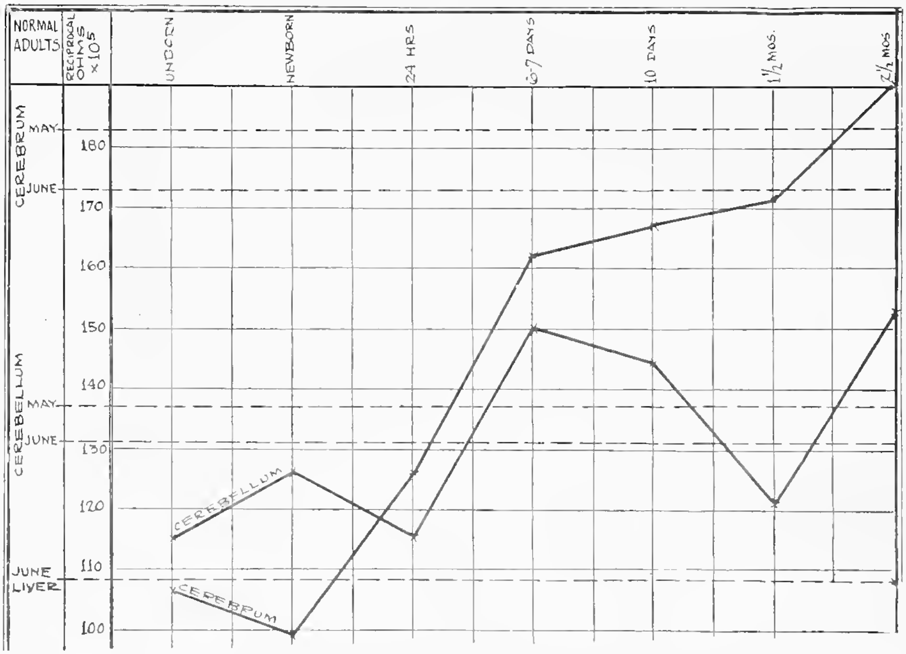


Fig. 84. Progressive Changes in the Conductivity of the Cerebrum and of the Cerebellum in Fetuses and in Young Rabbits.

These measurements were made between early May and late June. During these two months a variation in the normal conductivity of the cerebrum and cerebellum in normal adults was noted as indicated by the dotted lines on the chart.

ductivity of normal tissues appears to vary according to the season and the general environment—*i.e.* length of confinement, etc.

(2) Voluntary muscle has the highest conductivity of the tissues studied; the liver has the lowest conductivity.

(3) The conductivity of the normal adult cerebrum is higher than the conductivity of the cerebellum. In fetuses and in very young rabbits this relation is reversed—the conductivity of the cerebellum being higher than the conductivity of the cerebrum until about the time when the young rabbit

leaves the nest and begins voluntary activities, when the normal adult conductivity relation of the cerebrum and the cerebellum appears to be established

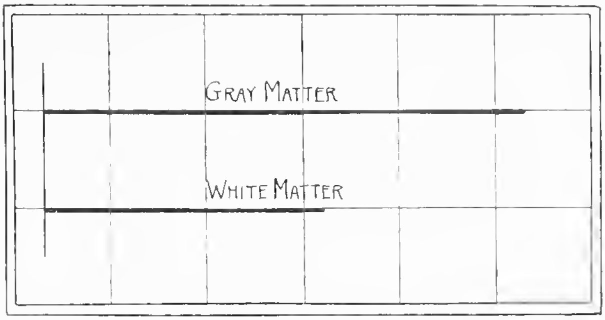


FIG. 85.—Relation of the Conductivity of the Gray Matter of the Cerebrum to the Conductivity of the White Matter. (Average Conductivities.)

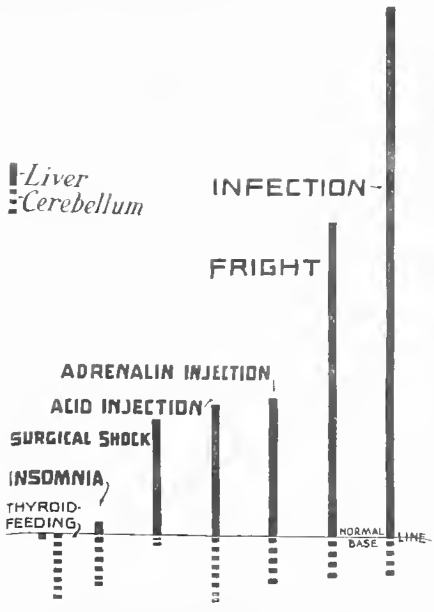


FIG. 86.—Percentile Variations from the Normal in the Conductivity of the Cerebellum and of the Liver in Exhaustion.

Note that in each case but one the conductivity of the liver was *increased* above the normal while the conductivity of the cerebellum was *decreased* below the normal.

(Fig. 84). A most significant corollary to this observation was found in the post-mortem examination of the brains of two patients, one of whom died after

days of unconsciousness resulting from a brain tumor, while the other, who died from carcinoma of the stomach, was unconscious to the end. In the patient who had been unconscious, *the conductivity of the cerebellum was higher*

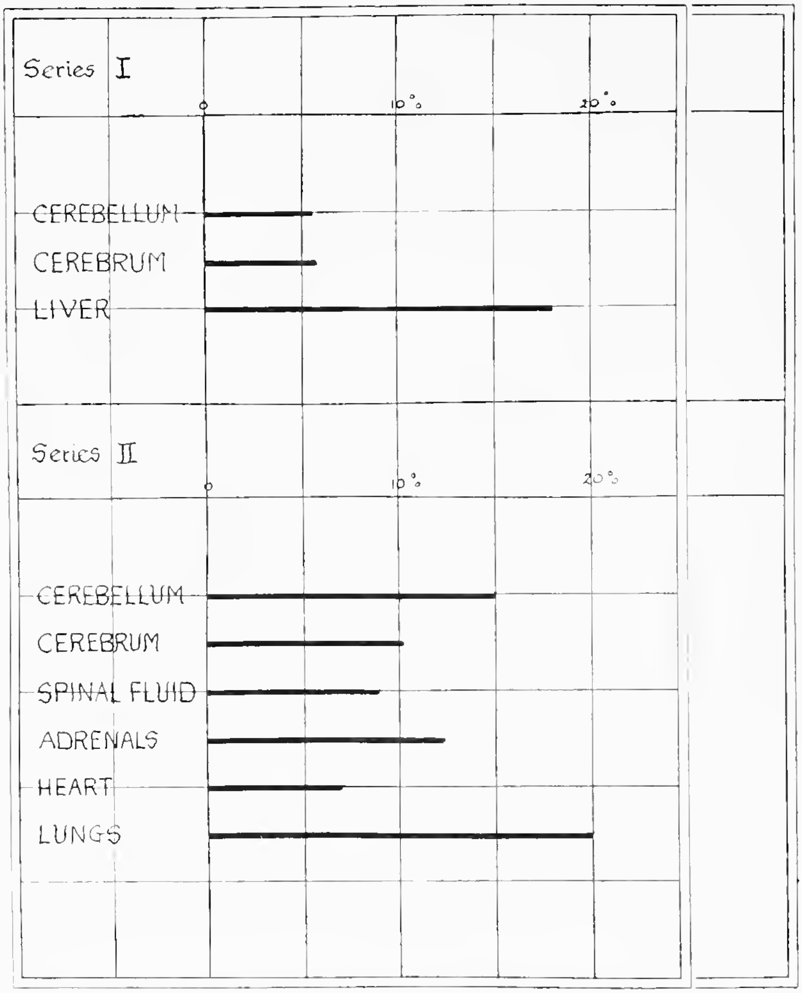


FIG. 87.—Relative Percentile Increase in the Electric Conductivity of Various Organs and Tissues Produced by Iodoform.

than that of the cerebrum. In the other patient, as in all our normal animals, the conductivity of the cerebrum was higher than that of the cerebellum.

(4) The conductivity of the gray matter of the brain is higher than that of the white matter (Fig. 85).

(5) Exhaustion from any cause—surgical shock, insomnia, emotion (fright), infection, etc.—is marked by *a diminished conductivity of the brain* and an in-

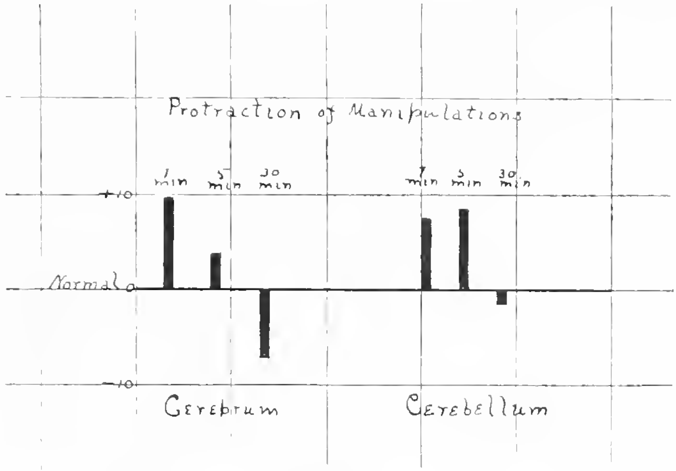


FIG. 88.—Percentile Changes in the Conductivity of the Cerebrum and of the Cerebellum after Varying Periods of Shock-Producing Manipulations.

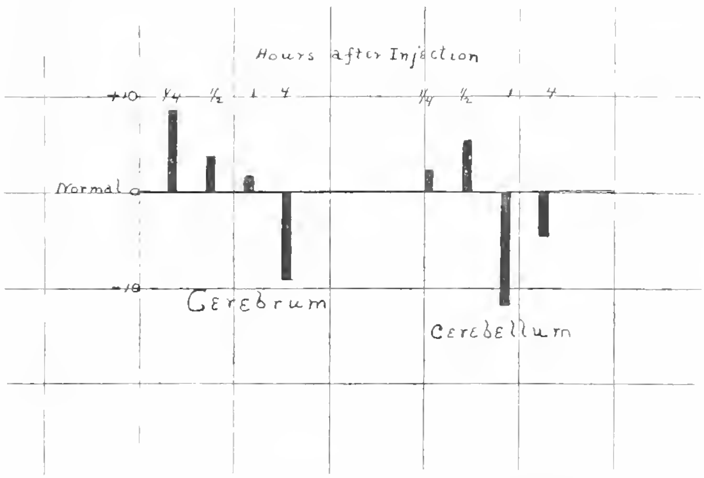


FIG. 89.—Percentile Changes in the Conductivity of the Cerebrum and of the Cerebellum at Varying Intervals after the Injection of Diphtheria Toxin.

creased conductivity of the liver (Fig. 86). With the exception of the liver the tendency of all the tissues in exhaustion is toward a diminished conductivity. Restoration, in particular when it is accomplished by long periods of rest

after insomnia, is marked by an increasing conductivity of the cerebrum and cerebellum toward the normal, and decreasing conductivity of the liver toward the normal.

(6) *Iodism.* Iodoform increases the conductivity of the brain, liver, spinal fluid, adrenals, heart and lungs (Fig. 87). In exhaustion produced by thyroid feeding the conductivity of the brain decreased and that of the liver increased as in exhaustion from other causes. A limited number of observations of the early effects of thyroid feeding, however, indicate an increased conductivity of the brain and also of the liver.

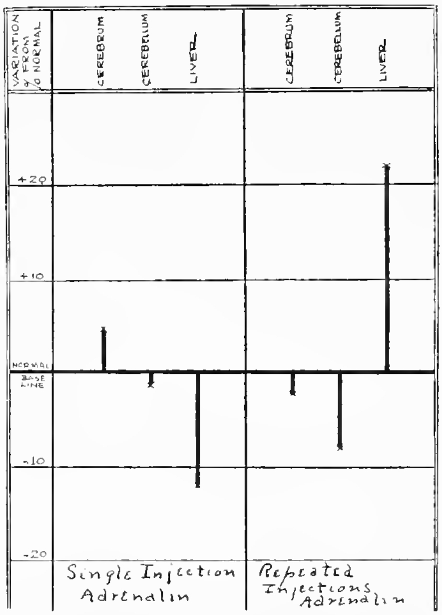


FIG. 90.—Percentile Changes in the Conductivity of the Cerebrum, of the Cerebellum, and of the Liver after Single Injection and after Repeated Injections of Adrenalin.

(7) *Incipient effects of stimulation.* The immediate effect of activation appears to be an increased conductivity of the brain, tending later to decrease as the stage of exhaustion approaches. As the charts indicate, this has been shown to be an immediate effect of physical injury; an early effect of the injection of diphtheria toxin; an immediate effect of the injection of adrenalin (Figs. 88-90).

(8) *Antithetic effects of acids and alkalis.* The injection of hydrochloric acid produced *diminished conductivity of the cerebellum and cerebrum and increased conductivity of the liver.* The injection of sodium bicarbonate produced

increased conductivity of the cerebellum and cerebrum and decreased conductivity of the liver (Fig. 91).

(9) *Restorative effects of sleep.* Rabbits were kept awake continuously for 96 hours. At the end of this period a number were killed and conductivity measurements made; others were allowed a brief period of rest; others a longer period of rest of from four days to a week. At the end of the insomnia period *the conductivity of the brain was decreased* and the conductivity of the liver

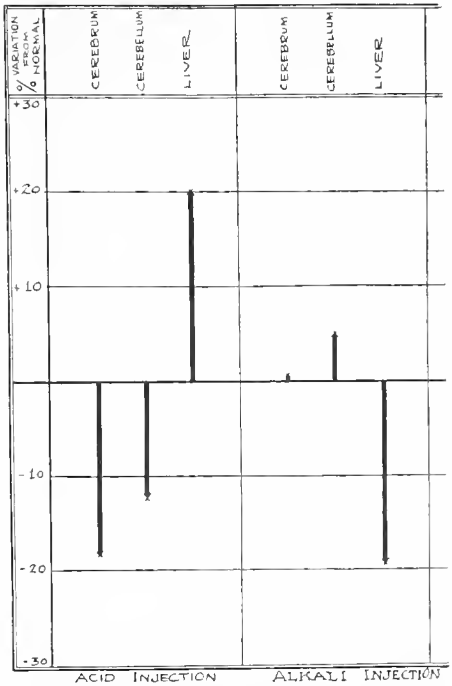


FIG. 91.—Antithetic Effects on the Conductivity of the Cerebrum, of the Cerebellum, and of the Liver Produced by Acid Injection and by Alkali Injection.

was increased; at the end of the short period of rest, the conductivity of the brain and of the liver was but little changed, if at all; at the end of the longer periods of rest, the brain and the liver were again approaching their normal conductivity (Fig. 92).

(10) *Protective effects of morphin.* A limited number of observations indicate that the changes produced by infection are minimised provided the infection is applied in the presence of morphin: that is, infection alone decreases the conductivity of the brain and increases the conductivity of the

liver; in this limited series of observations the conductivity of the brain remained practically unchanged when diphtheria toxin was administered in a

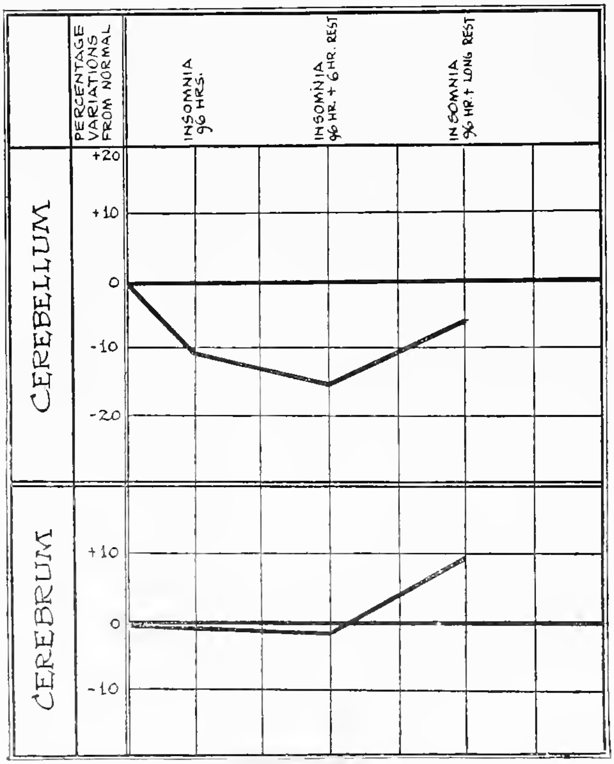


FIG. 92.—Restorative Effect of Rest and Sleep on the Brain-Cells as Indicated by Electric Conductivity Measurements. (Percentile Variations.)

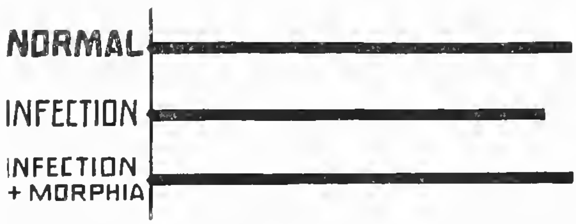


FIG. 93.—Protective Effect of Morphin in the Presence of Infection as Evidenced by Electric Conductivity Measurements. (Average Variations.)

morphinised animal, and the conductivity of the liver was but slightly altered (Fig. 93).

(11) *Pathological studies.* In the pathological specimens studied, active malignant growths have a high conductivity in comparison with the inactive portions of the same growth, and with growths of a non-malignant type.

From our findings to date, it would appear that the *intracellular changes in exhaustion and shock which are revealed by the microscope are paralleled by alterations in electric conductivity, and that both the histologic and the electric changes bear a direct relation to the vitality of the organ.*

CHAPTER II

THE MECHANISM OF EXHAUSTION

We shall now proceed to a discussion of the mechanism of exhaustion, based upon the summaries in the preceding chapter.

The man in acute shock or exhaustion is able to see danger, but lacks the normal muscular power to escape from it ; his temperature may be subnormal, but he lacks the normal power to create heat ; he understands words, but lacks the normal power of response. In other words, he is unable to transform potential into kinetic energy in the form of heat, motion, and mental action, despite the fact that his vital organs are anatomically intact. His mental power fades to unconsciousness ; his ability to create body heat is diminished until he approaches the state of the cold-blooded animal ; the weakness of the voluntary muscles finally approaches that of sleep or anesthesia ; the blood-pressure falls to zero ; most of the organs and tissues of the body lose their function.

It is evident, therefore, that in exhaustion the organism has lost its self-mastery. Self-mastery is achieved only by the normal action of the master tissue—the brain. In exhaustion, then, is the brain primarily exhausted ; or has some other tissue or organ functionally broken down, and has that breakdown carried with it exhaustion of the brain ? If the latter, then what organs and tissues are vitally necessary to the brain for the performance of its function ? Obviously, the exhaustion of any organ or tissue not vital to the performance of brain function need not be considered, since it probably would not be a direct cause of acute exhaustion.

I. Tissues and Organs Which Bear No Immediate Relation to the Problem of Acute Exhaustion

Among the tissues and organs that are not immediately vital to the brain, within the period of death from *acute* exhaustion, are the bones and joints, the connective tissue, the neutral fats, the skin, the genito-urinary system, the digestive system, the gall-bladder and ducts, the lymphatic vessels and glands, the salivary glands, the spleen, the sweat glands, the pancreas, the

thyroid, the thymus, the organs of common sensation, the nails, the hair. Want of activity of any of these organs or tissues individually or collectively cannot produce acute exhaustion in the sense in which that word is here used. That is to say, a man in exhaustion from the injury and the struggle of battle would not be restored if he were given rested eyes, rested ears, rested sweat glands, rested spleen, rested genito-urinary system, rested digestive system, rested bones and joints, rested connective tissue, rested skin, rested gall-bladder, rested fat.

II. Tissues and Organs whose Failure of Function may produce Acute Exhaustion

The tissues and organs whose failure of function may cause acute exhaustion are the respiratory system, the circulatory system, the blood, the muscles, the adrenals, the liver, and the brain.

RESPIRATORY SYSTEM

Relation of the Respiratory System to Shock and Exhaustion

The failure of the respiratory system to deliver sufficient oxygen to the blood, or to take sufficient CO_2 from the blood, exhausts and kills promptly. Failure of the respiratory system is not a universal, not even a common cause of exhaustion, for in the great majority of cases of exhaustion the respiratory activity is even increased, and there is no interference in the lungs with the exchange of gases. The interference with the pulmonary mechanism of air exchange that may cause exhaustion is most commonly produced by edema of the alveolar walls; by pulmonary embolism; by the exudations of pneumonia; by fat embolism; by the inhalation of water, or pus, or free blood; by excessive pleural effusion; by emphysema; by hemo- and pneumothorax. In each of these conditions there is interference with the intake of oxygen and the elimination of carbon dioxid which may be sufficient to cause exhaustion and death.

Theories Regarding the Relation of the Respiratory System to Shock and Exhaustion

Fat Embolism Theory

Roswell Park [1] first suggested and Bissell demonstrated the presence of fat embolism in the lungs of patients who were diagnosed as being in surgical

[1] Park, Roswell: *New York M. J.*, 1884, xl. 177-181.

shock. Porter[1] has extended Bissell's[2] observations into an inclusive theory of shock. He concludes that shock is due mainly to diffuse fatty embolism of the lungs. There are several facts that apparently are not harmonised by the fat embolism theory.

(*a*) In cases of abdominal penetration, if there is no perforation of the hollow viscera and no hemorrhage, there is little shock ; if there is either perforation or hemorrhage, or both, there is shock. Since, in either case, the same fat areas have been traversed, it follows that the traversing of the fat was not the determining factor.

(*b*) In emotional shock, so common in battle, it is difficult to assign to fat emboli a causative rôle.

(*c*) In shock from burns, the difficulty is no less.

(*d*) In shock from chest and head injuries, it is almost as difficult to assign a causative rôle to fat emboli. Many other examples may be cited.

On the other hand, surgical literature contains many accounts of the presence of fat emboli in fracture cases—especially fractures of the long bones, and these cases show no shock at first, but later develop a train of symptoms resembling shock.

Wiggers[3] performed a series of experiments to determine whether the mechanism which causes failure of the circulation after the intravenous injection of oil is the same as that which causes circulatory failure in surgical shock. He concluded that circulatory failure produced by fat emboli must be distinguished from circulatory failure due to surgical shock. The conclusions of Wiggers are in more complete accord with surgical experience than those of Porter. With respect to the CO_2 treatment which Porter[4] proposes, on the theory that the increased action of the diaphragm caused by the CO_2 would force the fat emboli out of the capillaries into the free circulation, it would obviously be difficult to determine how much of the clinical result might be due to pooling of the blood in the abdominal veins, for which Porter advises CO_2 inhalation, and how much to pulmonary fat embolisms, for which also he advises CO_2 inhalation. That is, would the clinical result be due to the pumping of the blood out of the abdominal vessels by the increased respiration induced by the inhalation of CO_2, or to the driving of the fat out of the lungs ; or would it be due to the relief of acapnia (Henderson)? But since in practice the CO_2 treatment has yielded no advantage to the patient, this point will not be pursued further.

[1] Porter, W. T.: *Boston M. and S. J.*, 1917, clxxvi. 248 ; 1917, clxxvii. 326-327 ; *Proc. Inst. Med.*, 1918, ii. 24-29 ; *New York M. J.*, 1917, cvi. 894-895.

[2] Bissell, W. W.: *J. Am. M. Ass.*, 1916, lxvii. 1926-1928 ; *Surg. Gyn. Obst.*, 1917, xxv. 8-22.

[3] Wiggers, C. J.: *J. Am. M. Ass.*, 1918, lxx. 508-511.

[4] Porter, W. T.: *Boston M. and S. J.*, 1917, clxxvi. 699, *et loc. cit.*

Henderson's Acapnia Theory

Yandell Henderson [1] has plausibly advocated the view that excessive ventilation of the lungs—resulting in excessive elimination of CO_2 from the blood—is the cause of shock. Since the respiratory centre is controlled largely by the CO_2 tension of the blood, it follows that in shock the respiratory exchange would be diminished, so that, as Henderson believes, there would result a state which is below the point of oxygen safety.

Henderson's theory is one which every surgeon would hope might be true, for apparently it would make both the prevention and the cure of shock easy and simple. There are many arguments in favour of this theory. The disturbing effect of excessive ventilation of the lung is apparent. It is true that oxygen improves the condition of the patient in shock, that lack of oxygen leads to acidosis. Nevertheless, there are certain difficulties in the way of accepting fully Henderson's conclusions.

(*a*) As we have stated above, the clinical use of CO_2 in shock has not proven to be of much value. It is possible that this is because serious intracellular damage has been inflicted upon certain vital organs before the CO_2 treatment was begun.

(*b*) In my laboratory, animals under curare and continuous adequate and even artificial respiration—thus eliminating the excessive ventilation (acapnia) factor—could still be killed by shock from trauma.

(*c*) Protracted consciousness—insomnia—in animals, subjected to no other excitement, causes complete exhaustion. Acapnia could scarcely be a factor here. It should be added that Henderson has not discussed this type of exhaustion.

Conclusion

In exhaustion from running, from fevers, from trauma, from anesthesia, from excision of the liver, from excision of the adrenals, from hemorrhage, from emotion, from insomnia, the exhaustion is not in any way related to the lungs. If there is a coexistent defect in the pulmonary function, by so much the more readily is exhaustion produced by trauma, by emotion, by fever, by exertion, by hemorrhage, etc. We therefore conclude that the primary cause of exhaustion may be found in the *pulmonary system, but that this is not a common primary cause.*

CIRCULATORY SYSTEM

Failure of the circulation exhausts and kills inevitably, and failure of the circulation is established sooner or later in acute cases of grave or fatal

[1] Henderson, Y.: *Am. J. Physiol.*, 1908, xxi. 126-156; 1908-1909, xxiii. 345-373; 1909, xxiv. 66-85; 1909-1910, xxv. 310-333, 385-402; 1910, xxvi. 260-286; 1910-1911, xxvii. 152-176; 1918, xlvi. 533-553; *Johns Hopkins Hosp. Bull.*, 1910, xxi. 235-240.

exhaustion. The question therefore is :—Is the failure of the circulation a primary or a secondary cause of exhaustion ; or is the circulatory factor sometimes a primary and sometimes a secondary cause ?

The Heart

The heart may be unable to pump the blood stream forcibly enough to maintain adequate circulation, in which case general exhaustion will occur as the result of lack of oxidation of the tissues. Exhaustion occurs clinically in the myocarditis of acute or prolonged infections ; as the result of excessive muscular exertion ; in anemia ; in the presence of valvular defects. But observations in both the clinic and the laboratory show that in surgical shock and exhaustion the heart muscle has not failed.

Distribution of Blood

Pooling in the Larger Veins

A number of observers have held the view that in shock the blood accumulates in various blood-vessels, this pooling becoming in effect an intravascular hemorrhage. There are certain facts, however, which are not harmonised by this theory.

(*a*) In the author's laboratory, experiments showed that shock could be produced in animals in which the abdominal vessels or the thoracic aorta were first excluded by ligation, though not quite as readily as in the controls. Erlanger[1] and others have shown that excision of all the abdominal viscera does not lessen the liability to shock. In our experiments we found also that if the intestines were so tensely distended with water as to drive out all the blood, then trauma of the peritoneum no longer caused a primary fall in blood-pressure but did not prevent death from shock. Many dissections before death, many autopsies after death from trauma to other parts of the body than the abdomen, showed that the blood was held in the veins everywhere, as in death from other causes.

(*b*) As stated in a preceding paragraph, Porter [2] has proposed the inhalation of CO_2 for the purpose of increasing activity of the diaphragm, to the end that thus the supposed accumulation of blood in the abdomen would be put into a more active circulation. No clinical advantage from this treatment has been reported.

(*c*) Treatment with intraperitoneal injections of pituitrin, as suggested by Cannon, even more effectively facilitates the splanchnic venous circulation

[1] Erlanger, J., Gesell, R., Gasser, H. S., and Elliott, B. L. : *J. Am. M. Ass.*, 1917, lxix. 2089-2092.
[2] Porter, W. T. : *loc. cit.*

than does Porter's CO_2 inhalation, but this method has not proved to be a cure for shock.

From the evidence in hand, we are not warranted in concluding either that blood does or that it does not pool. We only infer that even if it does pool, this is an end effect—not a primary cause of shock.

Accumulation of the Blood in the Capillaries

Cannon[1] has recently advanced strong arguments in favour of the view that the smaller blood-vessels—the capillaries—are dilated, and in dilating have engulfed so much of the volume of the blood as to seriously interfere with the circulation. If this were true, then the universal bandaging of the body alone, or blood transfusion alone, or bandaging and blood transfusion combined, should both prevent and cure shock. But both laboratory and clinical experience show that, although these measures are useful, they are not specific.

Vaso-Motor Mechanism

Is the vaso-motor mechanism a factor in shock ? In 1897 the theory that shock was due to the impairment or breakdown of the vaso-motor mechanism was proposed by the writer.[2] Owing to the fact that control of the blood-pressure did not specifically cure shock, it soon became obvious that exhaustion and shock included much in addition to the failure of the vaso-motor mechanism.

Opposing views as to the state of the vaso-motor mechanism have been presented by various investigators.

(*a*) Seelig and Lyon[3] have concluded that the vaso-motor mechanism is functionally intact in shock.

(*b*) Porter[4] has found that vaso-motor stimulation produces a progressively diminished rise in blood-pressure as shock deepens. This finding is in accord with our own data. Porter has interpreted the blood-pressure change on the basis of a percentile rise, and has concluded that the vaso-motor mechanism is not altered in shock. It is open to question, however, whether Porter has not proved the opposite of his conclusions, for if, in shock, adrenalin be given intravenously, or pressure on a paw be made, the percentile rise interpretation will be reversed. Applying Porter's percentile interpretation to the effect of adrenalin, the percentile rise would be over 300 per cent., that is, according to Porter's reasoning, the vascular state is three times better than normal, but nevertheless the dog is dying. The error in Porter's reasoning may be made

[1] Cannon, W. B., Fraser, J., and Hooper, A. M. : *J. Am. M. Ass.*, 1918, lxx. 526-531.

[2] Crile, G. W., *An Experimental Research into Surgical Shock*, 1897.

[3] Seelig, M. G., and Lyon, E. P. : *Surg. Gyn. Obst.*, 1910, xi. 146-152 ; *J. Am. M. Ass.*, 1909, lii. 45-48.

[4] Porter, W. T., and Storey, T. A. : *Am. J. Physiol.*, 1907, xviii. 181-199, xx. 399-405.

more clear by a homely illustration. If a goad be applied to a fresh horse, the resulting increase in speed may be stated as a percentile increase. When the horse is in extreme fatigue and an equal goad is applied, the percentile increase will probably be the same, but nevertheless the horse is exhausted.

(*c*) Erlanger[1] and his associates found that the vaso-motor mechanism is exhausted late in shock. They suggest that the primary fall in blood-pressure may be brought about by the effect of painful stimuli and hemorrhage.

(*d*) Pike and Coombs[2] believe that damage to the brain-cells must be included as one of the conditions of traumatic shock.

(*e*) Wiggers[3] observed a steady fall in vaso-motor tone in the early phases of shock. He concluded that the peripheral resistance was diminished, indicating diminished vaso-motor tone.

The experimental data reported in the preceding chapter (pp. 35-40) show that there is no practical distinction to be made between external stimulation of the vaso-motor centre as in injuries and operation, and internal stimulation by vaso-motor stimulants, as strychnin. Each in sufficient amount produces exhaustion (shock), and each with logic might be used to treat the shock produced by the other. We conclude, therefore, that in traumatic shock the vaso-motor mechanism is functionally impaired or exhausted.

Experience in the clinic, however, seemed to show that, whereas in shock the depression and fatigue of the vaso-motor centres were very important, there must also be other important effects. This was all the more probable because of the time required for recovery; the long after-effects; the inadequacy of merely raising the blood-pressure; the weakness and debility of the injured animal before a fall in blood-pressure had occurred; the fact that infection, loss of sleep, hunger and thirst predisposed to exhaustion; that ether anesthesia predisposed to exhaustion. All these clinical observations demanded renewed research. The work of Hodge on fatigue in bees and birds suggested such an investigation. To that end the studies of the brain-cells, which have been summarised in the preceding chapter (pp. 40-43), were undertaken. These studies immediately gave us illuminating results. Our argument was that if the vaso-motor centre was fatigued in shock and exhaustion, other parts of the brain were probably fatigued also. If the brain-cells were functionally altered, one would expect them to be physically altered, as Hodge had shown was the case in his studies of fatigue in the bee. We argued that in shock not only are the vaso-motor cells exhausted, but the cells of the brain that preside over voluntary muscular action and mental action are also altered; in other words, that the brain as a whole is altered, and is altered independently

[1] Erlanger, J.: *loc. cit.*

[2] Pike, F. H., and Coombs, H. C.: *J. Am. M. Ass.*, 1917, lxviii. 1892-1893.

[3] Wiggers, C. J.: *Am. J. Physiol.*, 1918, xlv. 485-499; 1918, xlvi. 314-328.

of, as well as in consequence of, the low blood-pressure due to the exhaustion of the vaso-motor centres; that the higher centres may well be affected even more than the vaso-motor.

The vaso-motor mechanism alone, the blood-pressure alone, is not sufficient to account for all the phenomena of shock; and although some of the causes of exhaustion may be found in the respiratory system, and some in the circulatory system, we must look elsewhere for the explanation of the vast majority of cases of shock and exhaustion. Are these due to some change in the blood?

The Blood

Chemical Changes in the Blood

The blood is a vital fluid for all the tissues. If there is insufficient blood, or if the blood is sufficiently impure, exhaustion of every organ and tissue will follow. The acute exhaustion caused by hemorrhage is cured in a normal animal by immediate replacement of the lost blood by an equal amount of good blood from another animal. If impure blood is the primary cause of exhaustion, and no other primary cause exists, then the removal of impure blood and the substitution of pure blood should bring relief from exhaustion in proportion to the amount of impure blood exchanged for pure blood. If exhaustion is due to some change in the blood, then if an acutely exhausted animal had its blood withdrawn as completely as possible and normal blood replaced, the same process being repeated several times so as to be certain that a sufficient amount of blood had been exchanged, demonstrable relief should follow. But experiments have shown that not many cases of exhaustion may thus be benefited or cured. Moreover, animals exhausted by insomnia show no change in the blood picture, as has been shown by our experiments. We have found, also, that in patients in whom exhaustion has developed gradually, there may be no change in the blood.

The common pathologic change in the blood in acute exhaustion is acidosis. If this were the primary cause of exhaustion, then infusion of sodium bicarbonate should prevent and cure; but both laboratory and clinical evidence shows that alkalis neither prevent nor cure shock.

Cannon[1] has found decreased reserve alkalinity in wounded soldiers in shock. He found this decrease was more marked in operations under ether than in operations under nitrous oxid; he believes that a diastolic blood-pressure of about 80 is a critical level at which acidosis rapidly develops. These phenomena are obviously secondary causes of exhaustion.

[1] Cannon, W. B.: *J. Am. M. Ass.*, 1918, lxx. 531-535.

Cannon, Dale and Bayliss [1] have recently found that the pulpefaction of muscles causes a fall in blood-pressure when the nerve supply of the injured part is blocked; and that this is prevented when the circulation of the part is blocked. Even so, macerated muscle products could be but a minor factor in the production of shock, for (*a*) tourniquets minimise shock only as far as they minimise hemorrhage; (*b*) spinal and local anesthesia almost specifically prevent shock; (*c*) many causes of shock, such as abdominal operations, joint injuries, skin injuries, etc., have no relation to muscle poison; (*d*) nitrous oxid anesthesia is all but a preventive of shock. How can these facts be reconciled with the view that the cause of shock is low blood-pressure, the low blood-pressure in turn being caused by muscle poisons? Even if under exceptional circumstances the presence of muscle toxins constituted a causative factor, their shock-producing value would be identical with that of the group of toxins, the effects of which have been previously studied and published. (See pp. 65-70).

Concentration of the Blood

The blood volume is apparently diminished in shock. Has the plasma left the vessels and gone into the tissues? If so, is this process an adaptation or is it a pathologic effect? This point was investigated in our laboratory by Drs. F. W. Hitchings, A. N. Eisenbrey, and C. H. Lenhart, who found that in shock the concentration of the blood was increased up to 20 per cent., but other considerations made it obvious that this is not a primary cause of shock.

'In the blood of the "shock" dogs there was an increase in the number of the red cells per cubic millimetre, while in the blood of the "hemorrhage" dogs there was a decrease in the number of red cells per cubic millimetre.

. . . .

'In the "shock" dogs there was a decrease in the number of white corpuscles, while in the "hemorrhage" dogs there was a preliminary decrease followed by a marked increase.' [2]

Mann [3] performed a more extensive research along the same line, and attributed greater importance to the increased concentration. Cannon [4] has shown further evidence of loss of plasma in shock, and supports Mann's estimation of the value of this data rather than our own. Now, if increased concentration were the cause of the small amount of blood, if circulatory failure were due to a 'plasma hemorrhage' into the tissue, then adequate transfusion of blood

[1] See reports of Special Investigation on Surgical Shock and Allied Conditions by the British Medical Research Committee, Special Report Series, 26.

[2] Crile, G. W.: *Hemorrhage and Transfusion*, 1909, pp. 82-83.

[3] Mann, F. C.: *J. Am. M. Ass.*, 1918, lxxi. 1184-1188.

[4] Cannon, W. B.: *loc. cit.*

should prevent and cure shock ; but adequate transfusion of blood is not a specific cure. In addition, on this theory, the careful work of Hogan and of Bayliss [1] on the infusion of colloidal solutions should have given us a cure, because it is known that these solutions do not leave the blood stream. But colloidal solutions fail to hold the blood-pressure—fail to cure advanced cases. The transference of plasma is probably an adaptive protection.

Then, again, even granting that the blood contains impurities which cause exhaustion, where did the blood get those impurities ? From the cells. And the cells ? From their increased metabolism. What caused that increased metabolism ? Certain of the excitants of exhaustion. We conclude, therefore, that in the absence of any primary disease which may cause changes in the blood, and in the absence of hemorrhage, changes in the blood or in the blood-pressure are a *secondary*, not a *primary* cause of exhaustion.

VOLUNTARY MUSCLES

If the voluntary muscular system were exhausted primarily in shock, then there would be prostration, low temperature, lowered blood-pressure, but not the extremely low blood-pressure often seen in shock, no sweating, no loss of mental symptoms. Therefore, it at once becomes apparent that primary exhaustion of the voluntary muscles could not be an adequate cause of *all* the symptoms of exhaustion.

Is exhaustion of the voluntary muscles the cause of the lowered body temperature ? Is the inability of the muscles to act due to a primary change in the muscles, while the brain is normal ? This seems improbable, for the following reasons :—

(*a*) The voluntary muscle is more resistant—more than fifty times as resistant to low blood-pressure and anemia as the brain (Crile-Dolley).

(*b*) The muscles in the acutely exhausted subject show no histological change. They can be made to contract by electric stimulation of their nerve supply, or by electric stimulation of the muscle directly.

(*c*) It is a physiologic axiom that voluntary muscles are not as readily exhausted as are the nerve centres that govern them.

(*d*) If there is primary exhaustion of the muscles, then, according to Bayliss, it would probably be due to the over-production of acid or other injuring by-products as a result of injury or of work performed. But in exhaustion from trauma under anesthesia, the muscles have done no work ; in exhaustion from fear, the muscles have done little work ; in exhaustion from overwhelming toxemia, there has been no muscular work. Finally, we know that in a vast

[1] Bayliss, W. M.: *Intravenous Injection in Wound Shock*, London, 1918.

number of the injuries which cause shock, no muscle is involved; *e.g.* injury of the skin, brain, knee-joint, hands or feet may result in shock.

We must, therefore, conclude that the voluntary muscular system plays a secondary, not a primary rôle in exhaustion. We have seen that the respiratory and the circulatory systems and the voluntary muscular system are sometimes primary causes of exhaustion, and frequently secondary causes. We have seen that in exhaustion all these tissues suffer a variable amount of disability, but the primary common cause of shock remains to be disclosed.

THE ADRENALS

The criteria for the objective study of the adrenals are the adrenalin output, the electric conductivity, and the histologic picture. Elliott,[1] Cannon,[2] and others have found an increased adrenalin output and a diminished adrenalin content in certain cases of exhaustion, *e.g.* in exhaustion due to inhalation anesthesia, to infections, and to emotion. Short[3] found no notable diminution in the adrenalin content in shock; Bedford[4] found no diminution of adrenalin output in shock; Mann[5] disassociates the adrenals from shock. In our laboratory we found cytologic changes in the adrenals in exhaustion from any cause, including insomnia, these changes being more marked in the cortex than in the medulla.

The Relation of the Adrenals to the Liver and to the Brain in Exhaustion

Apparently adrenalin alone can cause the brain to greatly increase its work. By cross-circulation experiments, we have found that adrenalin causes increased activity of the central vaso-motor mechanism (Figs. 94 and 95). Not only can adrenalin, as Cannon has shown, cause all the basic phenomena of exertion, emotion, infection, etc., but, as we have shown, it also causes brain-cell lesions identical with those produced by exertion, emotion, infection, etc., including the entire cycle of hyperchromatism, chromatolysis, swelling and even disintegration of the brain-cells. We know that when the adrenals are excised, the brain-cells undergo a progressive cytolysis, in which there is no primary stage

[1] Elliott, T. R.: *J. Physiol.*, 1905, xxxii. 401-467; *ibid.*, 1912, xliv. 374-409.

[2] Cannon, W. B.: *Bodily Changes in Pain, Hunger, Fear and Rage*, 1915; Cannon, W. B., and de la Paz., D.: *Am. J. Physiol.*, 1911, xxviii. 64-70; Cannon, W. B., and Hoskins, R. G.: *ibid.*, 1911-1912, xxix. 274-279.

[3] Short, A. R.: *Lancet*, 1914, i. 731-737.

[4] Bedford, E. A.: *Am. J. Physiol.*, 1917, xliii. 235-257.

[5] Mann, F. C.: *J. Am. M. Ass.*, 1917, lxix. 371-374.

of hyperchromatism, but an immediate and progressive chromatolysis, edema, and final breakdown.

From these facts it would appear that the brain is profoundly, even vitally, dependent upon the adrenals; that without the adrenals, the brain rapidly loses not only its functional power, but also its power of survival. How is the influence of the adrenals upon the brain exerted? Is it the result of the direct action of adrenalin on the brain-cells? Does adrenalin owe its effect upon the brain-cells to the resultant formation of an increased amount of oxyhemoglobin in the lungs, which was demonstrated by Dr. Menten;[1] or to its power of increasing the alkalinity of the blood? Or does adrenalin

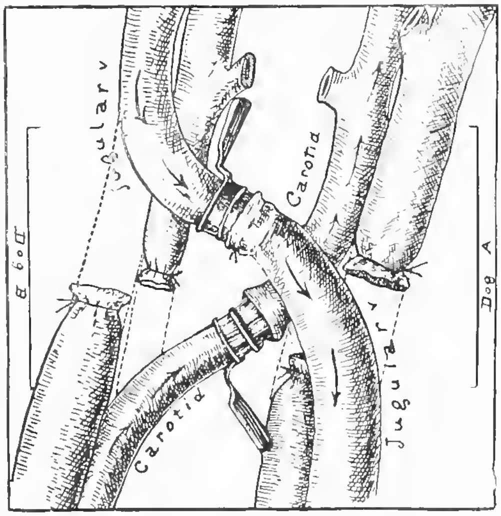


Fig. 94.—Schematic Drawing Illustrating the Anastomosis of the Circulation of Two Dogs. (See Fig. 95.)

owe its remarkable effect on the brain-cells to an intermediate effect on some other organ, such as the thyroid (Aschoff, Cannon), or the liver?

That the adrenals exert also a vital influence on the liver has been demonstrated by the cytologic changes produced by the intravenous injection of excessive amounts of adrenalin—chromatolysis, edema, displacement of nuclei, loss of the power of differential staining. Similar cytologic changes in the liver-cells follow double adrenalectomy. When the liver-cells are thus altered, from whatever cause, the brain is unable to do its work normally, and becomes exhausted. Assuming that the *absence* or the *excess* of adrenalin causes changes in the cells of the brain and of the liver, characteristic of exhaustion,

[1] Menten, M. L.: *Am. J. Physiol.*, 1917, xliv. 176-195.

then does adrenalin produce these changes in the brain-cells *primarily* by acting directly on the brain, or *secondarily* by first acting on the liver? It is known that adrenalin facilitates oxidation—hence it facilitates energy transformation, and therefore the internal respiration of the cells of each organ

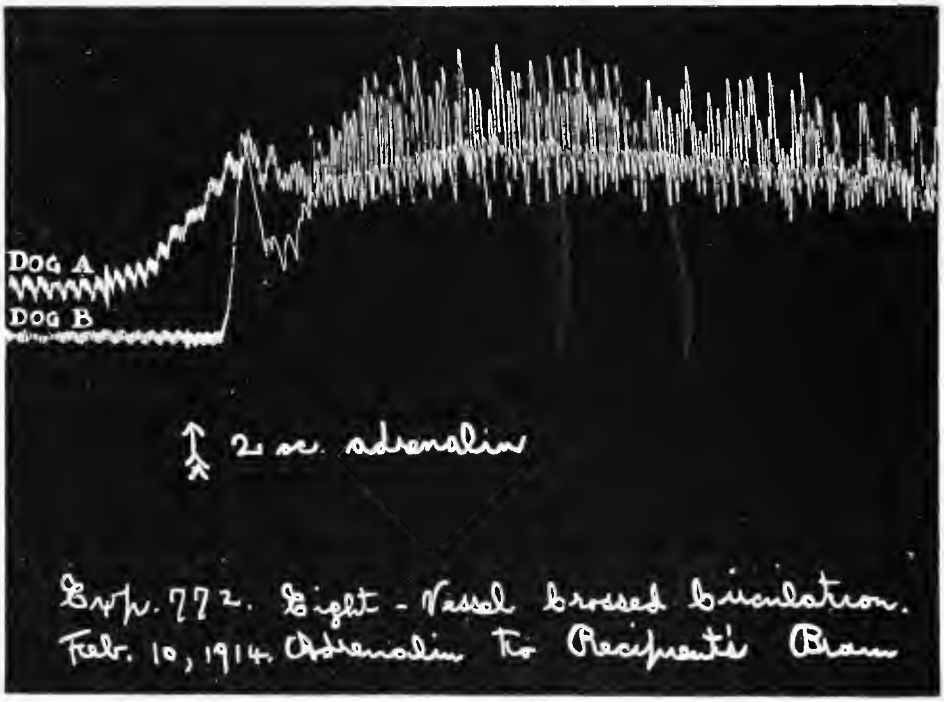


FIG. 95.—Blood-Pressure Tracing Showing Effect of Adrenalin on the Body of a Dog, whose Brain Alone Received Adrenalin.

The blood-pressure, taken from the carotid artery of dog B, *whose brain alone received the stimulus*, its body circulation being anastomosed to the brain of dog A, *which received no stimulus*, showed a sharp and immediate rise. The blood-pressure of dog A, *whose body alone received the stimulus* (see schematic drawing, Fig. 94), rose later, but to a lesser degree. The rise in blood-pressure of dog B is probably due to the fact that adrenalin acts directly upon some part of the brain, causing it to send energising impulses to the blood-vessels of the body, which result in a rise in blood-pressure.

An interesting feature of the rise in dog B was its unusual duration, as compared with the rise in an intact animal given an equal amount of adrenalin. The brain-cells of dog B showed hyperchromatism—the inference being that this hyperchromatism is an evidence of increased activity.

would be speeded up by the presence of adrenalin and diminished by its absence. The brain, being dependent on the functional integrity of the liver, and the liver being dependent in part on the adrenals, and each being dependent on oxidation, which in turn is, in part at least, dependent on the adrenals, we

must conclude that the liver and the brain are not only dependent on each other, but upon the adrenals as well.

We may conclude, therefore, that the adrenals are factors in the primary cycle of exhaustion, though their rôle cannot be accurately defined.

THE LIVER

Is the primary cause of exhaustion to be found in the liver? That the liver is necessary to the functional activity of the brain is proved by the following data:

(*a*) After excision of the liver, the power of the brain to drive the organism to transform potential energy into kinetic energy, such as heat or muscular or mental action, is rapidly diminished and completely lost at the time of inevitable death, usually within a few hours.

(*b*) The brain-cells show changes in their cytologic structure which are progressive from the moment the liver is excised.

(*c*) In every type of exhaustion from whatever cause, the cells of the liver show cytologic changes, such as diminished power of differential staining, edema, and increased electric conductivity.

(*d*) *Granting adequate circulation and respiration in a decapitated animal,* the excision of the liver causes death earlier than decapitation or adrenalectomy.

Some of the most important functions of the liver remain to be discovered, but there is one possible relation to which we may allude:—The brain-cells contain almost no stored carbohydrates or neutral fats; they contain almost no factors of safety against acidosis.[1] They have almost no stored oxygen. The brain-cells are almost wholly dependent on the blood for oxygen and for carbohydrate fuel to maintain their active and continuous metabolism; the blood is dependent on the liver for sugar for the brain. *Apparently,* for its protection against want of sugar, against intracellular acidosis, the brain is in part dependent on a long-distance connection with other tissues, especially the liver. The liver-cells are endowed with a great facility for autolysis; the brain-cells are but slightly subject to autolysis. We may suppose that the keen, stable brain-cells have a special chemical dependence on the remarkably unstable liver-cells. For opposite reasons, then, the two organs that are most susceptible to acidosis are the brain and the liver—the brain because of its extreme activity in acid production and because of *its lack of intracellular defence against acidosis,* of which more will be said later; the liver because of its avidity for acids, possibly an adaptation for the protection of other vital organs, especially the brain. If the brain-cells contained

[1] Mathews, A. P.: *Physiological Chemistry,* 1916, pp. 586, 589-592, 784-785.

space for the storage of reserve supplies of energy-producing material and protection against acidosis, in proportion to the space provided for this purpose in the cells of other organs, not only would the size of the brain be greatly and awkwardly increased, but its power to do work would be correspondingly diminished.

The integrity of the liver is essential to the work of the brain; and the integrity of the liver is also essential to the elimination of the acid by-products of metabolism by the kidneys and the lungs. When the liver is excised, the blood tends to become acid as the animal approaches exhaustion. The transfusion of blood, or the administration of adrenalin or of morphin, exerts not the least check on the exhaustion and death which follow excision of the liver. On the other hand, decapitation apparently does not interfere with the function of the liver.

For its oxidising and reducing power, the liver apparently depends, in part at least, on the adrenals; for, as we have stated above, the excessive intravenous injection of adrenalin on the one hand, and adrenalectomy on the other, cause marked cytologic changes in the liver-cells — chromatolysis, edema, eccentric position of the nucleus.

In our electric conductivity studies we found that in exhaustion from any cause the liver and the brain were affected in opposite directions, *i.e.* in extreme exhaustion the conductivity of the brain was decreased, and the conductivity of the liver was increased. In the earliest stages of stimulation these changes were reversed, the period of increased conductivity of the brain apparently corresponding to the period of hyperchromatism established by our histological studies.

From these premises we conclude that the liver is inseparably associated with the brain and the adrenals in the production of shock and exhaustion; but as the liver has no means of immediate contact with the external excitants of shock and exhaustion, it apparently in some way is influenced indirectly through the mediation of the brain.

We have now seen that *exhaustion* may be produced both *primarily* and *secondarily* by anatomical and functional defects and disabilities of the *respiratory system*, of the *circulatory system*, of the *blood*, of the *liver*, of the *adrenals*. We have seen that in exhaustion these organs and systems share in the general debility, but we have not been able to show that functional impairment of any one or of any combination of these is the sole cause of the exhaustion of the organism in exertion, in emotion, in injury, in infection, in enforced loss of sleep, etc. If, then, the primary cause of exhaustion is not disclosed in the study of these important organs and tissues, which are either directly or indirectly driven by the master tissue, the brain, we may then ask: Is the primary cause of exhaustion to be found in the brain? Has the brain

inherent elements of weakness greater than those of any other organ or tissue of the body?

THE BRAIN AND THE NERVOUS SYSTEM

The Brain as an Energy-Transforming Organ

Environment, external and internal, drives the brain; and the brain either directly or indirectly drives the entire organism. Is the brain tissue itself a transformer of potential energy into kinetic energy, and does it drive the body by means of some familiar form of energy which it creates, or does the brain drive the body as a mystery organ obeying no physical laws? Is the brain capable of exhausting itself primarily by its own excessive work, or is it only secondarily exhausted?

Do the brain-cells transform much or little energy? Are they active or inactive cells? That the brain transforms potential into kinetic energy, and by means of that energy drives the body, is shown by the failure of power to act when the head is cut off. That the brain is not only an active, but *the most active energy-transforming organ of the body*, is held by Mathews.[1]

The following reasons for this view are advanced:—

(*a*) The rudiments of the brain and of the eyes are the first structures of the vertebrate embryo to appear.

(*b*) Child[2] has shown that even in the embryo the brain leads all other tissues in growth and development, and, like the bud of the plant, has the highest metabolism.

(*c*) The brain has a more abundant arterial blood supply than any other organ except the adrenal (Neuman[3]). Not only does it possess a vast blood supply, but the arteries and capillaries are so distributed as to ensure a plentiful and constant blood supply. This is seen in the system of paralleling arteries, reinforced by the great basilar arterial distributor—the circle of Willis—which forms an abundant basal supply such as is provided for no other tissue or organ of the body. This is sufficient proof of the brain's intense need for oxygen and for the elimination of waste.

(*d*) The blood that flows up into the brain is arterial blood, and the blood returning from the brain is venous blood. In its momentary journey through the brain, large amounts of oxygen are taken out of the blood and large amounts of CO_2 are added.

[1] Mathews, A. P.: *Physiological Chemistry*, 1916, pp. 563-565, 584-595.

[2] Child, C. M.: *Proc. Nat. Acad. of Sc.*, 1915, i. pp. 164-172.

[3] Neuman, K. O.: *J. Phys.*, 1912, xlv. 188-196.

(*e*) There is more sugar in the supplying artery than in the returning vein. The sugar is burned in the brain.

(*f*) The brain is singularly dependent on the oxygen in the blood, since consciousness is lost within a few minutes after the lung has ceased to take in oxygen. The great dependence of the brain on atmospheric oxygen may be correlated with the fact that there are no stored carbohydrates in the brain. For the brain, six minutes of complete interruption of the blood circulation is the critical period, after which life cannot continue, in contrast with approximately five hundred minutes for muscles (Crile-Dolley).

(*g*) The brain is more sensitive to cyanides than any other tissue of the body. This is significant because of the fact that the tissues which are most dependent on atmospheric oxygen are most sensitive to drugs which have a great affinity for oxygen, such as the cyanides.[1]

In addition to the above, the following further evidence may be cited :—

(*a*) When the hydrogen-ion concentration of the blood is increased by anesthetics, such as ether, chloroform, nitrous oxid, until the neutral point is passed and acidity is established, the action of the brain—and life—ceases (Menten-Crile). There is evidence that the brain is more sensitive to acids than any other tissue, for in acute acidosis the function of the brain is lost earlier than that of any other organ.

(*b*) Interference with the use of oxygen by nitrous oxid causes unconsciousness within thirty seconds. Consciousness, then, depends on oxidation, *i.e.* on energy-transformation, just as engines and motors depend on oxidation for their energy-transformation.

(*c*) The work of the brain is greater in proportion to the weight of its tissue than is the work of any other organ of the body. Alexander and Cserna state that the brain shows a consumption of 0·360 cc. of O_2 per gram minute, while voluntary muscle showed a consumption of only 0·004 per gram minute. According to these observers, a given weight of brain tissue transforms energy about ninety times as rapidly as an equal weight of the voluntary muscles in the quiescent state. The voluntary muscles constitute 42 per cent. of the weight of the body, the brain 2 to 3 per cent. Hence, according to the findings of Alexander and Cserna,[2] excepting when the muscles are active, the brain has a total metabolism five times greater than the metabolism of all the voluntary muscles together.

From these facts we conclude that the brain is an organ of intense metabolism. Are the brain-cells safeguarded against the factors of exhaustion ? Has the brain any peculiarities that suggest an answer to this query ?

[1] Mathews, A. P. : *Physiological Chemistry*, 1916, p. 590.
[2] Alexander, F. G. : *Biochem. Ztschr.*, 1912, xliv. 127-139.

Special Features of the Brain-Cells

Among the unique features of the brain-cells are the following (see Mathews) :—

(*a*) The tips of the dendrites are liquid (Harrison[1]); and Hegar[2] states that they have the power of movement. These may constitute a mechanism associated with alternating work and rest.

(*b*) The cells of the brain are the only cells of the organism that have no stored carbohydrates and no neutral fat. Stored carbohydrates in other cells are the source of anaerobic oxygen. They supply energy in the absence of atmospheric oxygen ; they supply oxygen for neutralising lactic acid, and for overcoming intracellular acidity. The brain-cell, therefore, has within itself no stored fuel, no protection against want of aerobic oxygen.

(*c*) Unlike muscle, liver, and other tissues, the brain depends exclusively on *aerobic* oxidation. This should render the brain-cells vulnerable ; it accounts for the peculiar susceptibility of the brain to cyanides ; it may well be the reason why the brain-cells are more susceptible to nitrous oxid than any other cells, this property conferring on nitrous oxid the property of an anesthetic.

(*d*) There is less protein in the brain-cells that can be broken down as a protection against acidosis than in any other cells of the body, another point of weakness in the brain-cell. The brain-cell lacks protection against the acute carbon dioxid intoxication of exertion, fever, emotion, etc.

(*e*) The brain-cells have no power of autolysis. This lack of the power of autolysis is another source of danger.

(*f*) The brain-cells have no basal metabolism except that of energy-transformation, associated with work. After the brain-cells have reached adult size, they have no further power of growth. The brain-cells are permanent mechanisms.

(*g*) If a brain-cell is destroyed, no other brain-cell takes its place ; its loss is permanent.

(*h*) Since the brain-cells are the master cells of the body ; since they are the most highly receptive cells ; since they have the most active metabolism ; since they possess no internal mechanism for protection against deprivation of oxygen, against acidosis, or against starvation, one would expect to find that ample protective mechanisms against these vital dangers to the brain have been evolved in other parts of the body. In support of this suggestion is the fact that when the body loses weight through starvation, the brain itself loses no weight (see Voit's tables), but through its avidity for energy draws

[1] Harrison, R. G. : *J. Exper. Zool.*, 1910, ix. 787-846.

[2] Mathews, A. P. : *Physiological Chemistry*, 1916, p. 583.

from every other organ and tissue except the heart muscle. The nation at war feeds its soldiers first.

It would appear that the brain-cell is evolved, stripped to its decks, to fight the battle of life; as if its function as an energy-transformer were so important that certain means of defence are withheld from the brain-cell and provided for it by other organs, *e.g.* protection against intracellular acidosis, against want of oxygen, against want of food. It would seem, therefore, that these vital functions are committed to other organs. The vast volume and distribution of blood in the liver, in the lungs, and in the kidneys provide for the rapid elimination of waste which is urgently necessary, especially for the safety of the brain. The extreme avidity of the liver-cells for acid metabolites, coupled with the immense cellular surface exposed to the blood stream, we conceive to be one of the greatest safeguards to the brain against acidosis. The large storehouse of sugar in the liver serves as the fuel depot for the brain and as a protection against want of anaerobic oxygen. The blood stream carries oxygen and sugar to the brain; the buffer substances of the blood are a continuous protection to the brain against intracellular acidosis. *The brain-cells may be conceived as having their protective and nutritive cytoplasm evolved to function at a distance.*

From the elaborate provision for its protection, we may infer that the energy-transforming function of the brain has such high selective value in the biologic sense as to confer a selective value also on the structure and function of the liver and of the blood; for if the brain-cells, thus stripped, cannot transform energy fast enough to drive the muscles speedily enough to escape from the enemy, then the liver and the blood will perish as well as the brain. The more completely the liver and the blood and the lungs and the kidneys keep the brain-cells free from the impairing by-products of their active metabolism, the cleaner pair of heels will the pursuing enemy see. It would seem that if the bulk of the brain-cells were increased by stores of lifeless food. their power of attack and defence would be diminished.

(*i*) The brain cannot work continuously, but a reversible process is necessary at regular intervals to restore it. This process in the higher centres is called sleep. The more intense the activation, the more needed is sleep. The brain is the only organ that sleeps conspicuously. Of great significance is the fact that the entire man spends one-third of his time waiting for the brain to restore itself—to put itself again in the position of being able adaptively to transform potential into kinetic energy. This point will receive further consideration in a later section.

(*j*) The dominating importance of the brain is further shown by the fact, as Mathews [1] has pointed out, that natural selection in the higher animals

[1] Mathews, A. P.: *Physiological Chemistry*, 1916, pp. 563-564.

has centred on the brain and on the brain alone. Higher animals compete through their brains. Hence, in the brain-cells, we have the highest development of a mechanism for transforming energy, for securing survival through adaptation.

We may conclude by repeating Sherrington's statement that *the brain is the master tissue of the body*. We have seen that the brain is the most active energy-transforming tissue of the body. We may conclude that when we speak of *exhaustion of a man*, we mean *exhaustion of his brain*. This is the central fact.

Is Exhaustion of the Brain Primary or Secondary, or Both?

There is evidence that the brain is both primarily and secondarily involved in exhaustion. Common experience demonstrates that sudden bad news, intense fright, sudden severe pain, acute overwhelming infection, cause an immediate loss of muscular and mental power. Further evidence of the diminished power of the brain to do work in the presence of an adequate blood-pressure and respiration is seen during the early stages of physical exertion, of emotion, of fever, of insomnia, etc. Athletes in the early stage of the contest show no diminution of blood-pressure, but they do show diminished mental power.

In shock-producing trauma of animals under anesthesia, it was usually half an hour before the blood-pressure began to decline. What would be the physical power of an animal thus traumatised and disembowelled were he allowed to recover from anesthesia, even though his blood-pressure were normal? Captain Cowell[1] found that the average blood-pressure of soldiers on active trench duty was above normal; but despite their high blood-pressure, these soldiers nevertheless had to be relieved for rest because of their fatigue.

In the course of fevers, the blood-pressure is usually higher than normal, but the man is prostrated. In the midst of acute grief or worry, the blood-pressure may not be reduced, but the power of the brain is reduced. A rabbit under intense excitation shows a blood-pressure higher than normal, but its brain-power is diminished. A brilliant student, a great military strategist, a highly trained executive may suffer a breakdown from mental overwork and be in a state of brain exhaustion, yet the blood-pressure may be normal. In the experimental laboratory, in the clinic of life, in the stress of war, we have reliable data from which we conclude that the brain may be exhausted primarily while the blood-pressure may be normal, or even higher than normal. The brain is primarily exhausted in insomnia, in which probably acid by-products are not produced faster than the body is able to eliminate them. The brain

[1] Cowell, E. M.: *J. Am. M. Ass.*, 1918, lxx. 607-610.

is primarily exhausted by anesthetics, by cyanides, by acids, by lack of oxygen, by direct or reflex electric stimulation, by the excision of the adrenals, by the excision of the liver, etc. On the other hand, neither the brain-cells nor any other organ, nor the individual as a whole, is immediately exhausted by unlimited trauma *inflicted on areas cut off from connection with the brain by blocking the nerve supply.*

To a less degree, but markedly, is exhaustion from trauma or emotion controlled by large doses of morphin, or by nitrous oxid. Nitrous oxid diminishes the oxidation of the brain-cells, and hence the brain is less driven by trauma. When exhaustion or shock from trauma is *prevented* by blocking the nerves, or when the nerves are intact but the brain-cells are *prevented* from being excited to action by nitrous oxid, not only is the brain protected, but the liver, the adrenals, and other organs are equally protected; the blood-pressure does not fall, and the individual as a whole is protected against exhaustion. But despite the fact that the brain is the primary factor in both work and exhaustion, the brain is affected also by many secondary causes of exhaustion—defective circulation, insufficient lung ventilation, low blood-pressure, anemia, blood acidosis, hemorrhage, lack of oxygen, disease of the liver, disease of the adrenals, etc.

Apparently the more chemically receptive and reactive the tissue, and the more highly it is evolved to transform energy, the more readily is it exhaustible. A ligament, a nail, a tooth cannot produce heat or motion or electricity or a secretion—they are not exhaustible. Only cells have the power of transforming energy. The cell being the unit of work, the cell equally is the unit of exhaustion, and the brain-cell is the most readily exhausted. What, then, has happened to the brain-cell in exhaustion?

CHAPTER III

THE INTRACELLULAR PROCESS OF EXHAUSTION

I. Protective Mechanism against Intracellular Acidity

We have seen that among the changes—and there are other important changes—in the cells in exhaustion, there is evidence of increased intracellular acidity. If intracellular acidity constitutes a functional damage to vital organs, then it has selective value, and certain mechanisms must have been evolved as a protection against it.

All normal active cells have a similar pattern of structure. The nucleus is more acid than the cell body.[1] The difference of potential created by this difference in reaction is apparently necessary not only for the performance of the work of the cell, but also for its survival. That the defence mechanism against excessive acidity of the rest of the cell apparently has survival value is indicated by the fact that, *excepting in the case of the brain-cells*, all cells are provided *within themselves* with an efficient mechanism of defence against acidosis. Whenever the acidity of the cytoplasm and of the nucleus becomes equalised, whether as a result of normal processes or of the intravenous injection of acids in consequence of which the elimination by the cell of its metabolised acid is delayed or prevented, the cell then can do no work—it is exhausted. The development within the cell of a difference in reaction and in consequence of a difference in potential between the cytoplasm and the nucleus, is one of the foundation-stones on which life depends. The constant production of acids in the cytoplasm as a part of the process of living tends to kill the cell. It has been shown that blood corpuscles, which at the normal acidity of the blood ($H=2{\cdot}56\times10^{-8}$) carry a negative charge, become electrically neutral when the acidity of the blood increases to an H-ion concentration of $1{\cdot}25\times10^{-5}$.[2]

The following phenomena, most of which are pointed out by Mathews, may be noted :—

1. The reaction of living cells is approximately the same as the reaction of blood.

[1] Pentimalli, F.: *Arch. f. Entwcklngsmechn. d. Organ.*, 1912, xxxiv. 444-451; McClendon, J. F.: *Proc. Soc. Exp. Biol. and Med.*, 1910, vii. 111-112.

[2] Michaelis, L.: *Die Wasserstoffionenkonzentration*, 1914; Michaelis, L., and Takahashi, O.: *Biochem. Zeitsch.*, 1910, xxix. 439.

2. At the outset of acidosis, *except in the case of the brain-cells*, autolytic enzymes appear in the cell—both proteolytic and carbohydrate and carboxyl-splitting enzymes.

3. That the above are adaptive changes is indicated by the fact that by means of the carbohydrate-splitting enzymes, the cells, *excepting the brain-cells*, obtain glucose and levulose from glycogen, from cane sugar, and from other carbohydrate reserves. By the aid of the anaerobic oxygen from the glucose and levulose the cells of the body, *excepting the brain-cells*, are able in spite of the lack of aerobic oxygen to carry on their respiration and oxidation in the presence of acidosis which otherwise they could not withstand.

In the liver, glycogen is similarly transformed into glucose for the protection of the internal respiration. The *brain*, however, as previously stated, has no reserve store of carbohydrates, and could not make use of these enzymes for this purpose.

4. The proteolytic enzymes attack the protein of the cell, setting free ammonia by means of which the cell acids are neutralised. Here again the brain-cell is at a disadvantage, for it has no replaceable protein that can be thus used.

Thus, in every tissue of the body *excepting the brain*, acidosis is attended by an immediate proteolysis in the cells with the appearance of ammonia, which neutralises the acids.

5. The edema of the cells characteristic of increased acidity of cytoplasm may be regarded as an adaptation, since it tends to dilution and consequent reduction of the hydrogen-ion concentration.

6. The protein constituents of the cells—none of which can be spared without injury in the case of the *brain-cells*—have the power of combining with acids and neutralising them.

7. In the digestion of the proteins amino-acids are set free. By means of these, the acids are in part neutralised as by ammonia, by the formation of salts. In addition, by means of the carboxyl-splitting enzymes or carboxylases the carboxyl group is split off, and there remains a base which has a much greater power of combining with acids than the amino-acids themselves. This process pertains to all the cells of the organism, *with the exception of the brain-cells*.

8. Inorganic safeguards against acidosis are the *carbonates and phosphates* of the blood, which act as buffers. By means of these the blood is able to take up considerable amounts of acid with but slight change in its own acidity.

Sodium acetate has a similar power. Carbonic acid and phosphoric acid are very weak acids, so that when acids such as lactic or oxybutyric acid are found in the cells, the latter at once take the base away from the carbonates

and make a bicarbonate which is scarcely acid at all. Other weak acids are held in reserve.

9. Fatigue develops more readily when alkalinity is much reduced.

10. Athletes fill their blood with oxygen to facilitate oxidation of waste products, thus minimising acidosis.

11. Muscular exertion produces lactic acid, which is reduced by oxidation; if unreduced lactic acid remains, there is fatigue.

From these facts we deduce that, as compared with other cells, *the brain-cells possess but little intracellular protection against acidosis.* From this deduction three inferences are drawn :—

1. That there are certain mechanisms outside the brain designed for its protection against acidosis.

2. That the function of the brain-cell is so unique, so different from that of other cells, that the brain-cell cannot store food and protective materials within itself.

3. That acids must serve a useful purpose to the brain-cell in the performance of its specific work.

II. Do Acids Play a Rôle in the Function of the Cell?

From the foregoing we conclude that the vast protective mechanism which was evolved as a protection against intracellular acidosis indicates that since a process having such dangers has been evolved, then it must have selective value—it must be vitally useful. Animals never evolve a menace to themselves—only advantages are evolved. What, then, is the biologic advantage to the organism which results from the presence of acids in the cells —what is the vital *benefit* and what is the vital *danger* of the H-ions in cell processes ?

It is probable that oxidation and the consequent acidity are parts of the most fundamental processes in the cell ; that the H-ions and the OH-ions are agencies by which the cell is stimulated to do work. The intracellular acids produced by oxidation are probably a part of the mechanism which fabricates electric energy. The acids and bases of batteries are essential to the creation of electric energy. The H-ion, upon the presence of which acidity depends, is the smallest and the most swiftly moving ion. Consequently, when H-ions are formed in the cell by oxidation, they are the first ions to reach the cell boundary.

It is probable that the H-ions play an essential rôle in the creation of energy within the cell ; and it is possible that the intracellular acid which results from

oxidation within the cell may play a rôle similar to that played by hydrochloric acid in a battery with metal poles. In this analogy the nerves would correspond to the copper wire which Sir William Ramsay has stated is permeable to electrons but not to metal ions. Thus, as Ramsay has said, the copper terminal constitutes a semipermeable membrane. In the biologic cell battery, also, there are semipermeable membranes. Such a conception suggests further the brain-cell's lack of neutralising agents within itself, for the intracellular acid may serve as an essential element in making the brain-cell an efficient battery.

Intracellular acidosis is not the only change in exhaustion, for if an animal in exhaustion or in acidosis resulting from hydrochloric acid poisoning is given sufficient alkali to re-establish the stainability of the cell, *the exhaustion is by no means overcome.* That alkaline restoration is largely a veneer is indicated also by the fact that the power of the brain-cells to receive alkaline stain is soon lost, provided the animal is not allowed to sleep. If allowed to sleep, then the alkaline stainability will be quickly restored.

Even the intracellular changes caused by hydrochloric acid poisoning are overcome only during sleep (Figs. 96-98). Since the body cells act like batteries and since electric batteries, during action, exhibit the continuous passage of ions in such a direction as will deplete the original store of energy and lower the capacity of the battery for doing further work, or in other words in such a direction as will depolarise the cells, it follows that sleep, and sleep alone, can accomplish restoration of the original condition or repolarisation.

III. Physico-Chemical Consideration of the Intracellular Mechanism of Exhaustion

If we accept the view of physicists and biochemists (Du Bois-Reymond, Nernst, Bethe, Lillie, McClendon, Mathews, Osterhout, Loeb, Bernstein, A. V. Hill, Wm. Ostwald, Piper, MacDonald, Meyer, Crehore and Williams, and many others), that the functions of cells relate to electrical processes, new points of departure in our further consideration of exhaustion are opened.

It was such a conviction that led me to enlist in our researches the coöperation of two physicists, G. B. Obear, of the Case School of Applied Science, and Miss Helen R. Hosmer. The findings in this research have been reported in Chapter I. The data we desired from these physicists bore the following relation to our preceding work :—

We had long pursued and at last established a constant relationship between exhaustion and certain physical changes in the cells of certain organs, especially of the brain and the liver. We wished to know if the physiologic exhaustion

and the histologic changes were accompanied by parallel changes in electric conductivity. The histologic changes in the cells, and the exhaustion of the entire individual, could be achieved either by an extremely short period of intense activity or by a long period of mild activity. We wished the physicists to tell us whether or not there is physical evidence that intense short applications of strong stimuli produce the same changes in the organism as

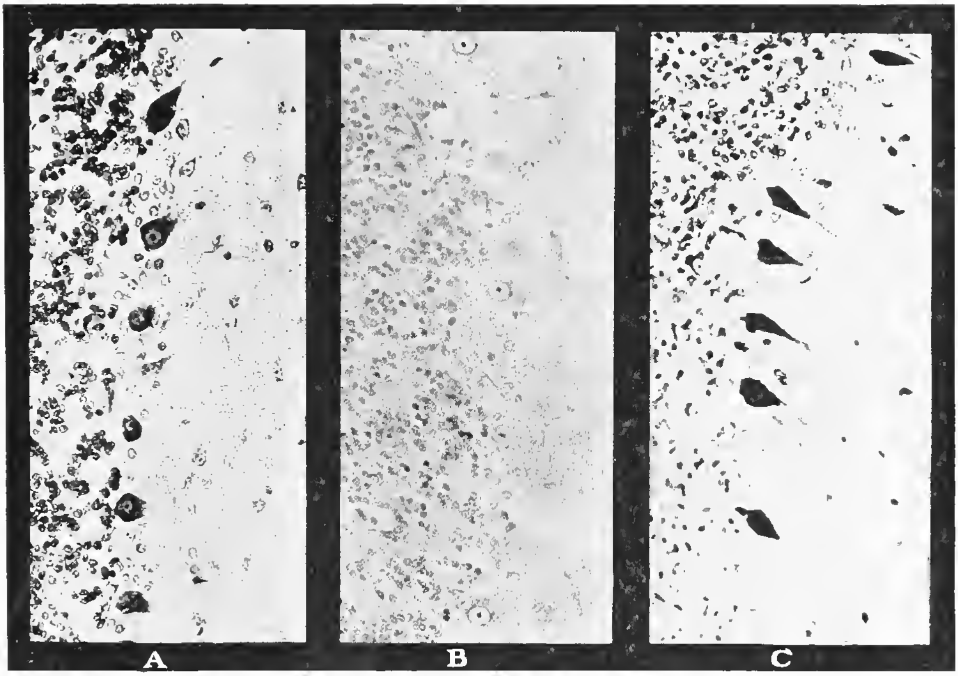


Fig. 96.—Restorative Effect of Sleep in the Presence of Acidosis.

A, Section of normal cerebellum.
B, Section of cerebellum after the intravenous injection of hydrochloric acid.
C, Section of cerebellum when the animal had had a prolonged period of sleep after the injection of hydrochloric acid.

(From photomicrographs, × 310.)

are produced by the prolonged application of weaker stimuli. The edema of the cells was interpreted as being due to changes in electrolytic concentration. Certain physical changes in the cells, at least, should be detected with even greater accuracy by determination of the electric conductance than by microscopic examination.

The salient facts established by this part of our research are :—

1. The conductivity of the cerebrum is higher than the conductivity

of the cerebellum excepting in the fetus (in the rabbit) and earliest days of extra-uterine life, *when this relation is reversed, the conductivity of the cerebellum of the fetus being higher than that of the cerebrum.* This reversal is apparently *coincident with the beginning of conscious activity.*

2. In extreme exhaustion from any cause, the *conductivity of the brain is decreased, and the conductivity of the liver is increased.*

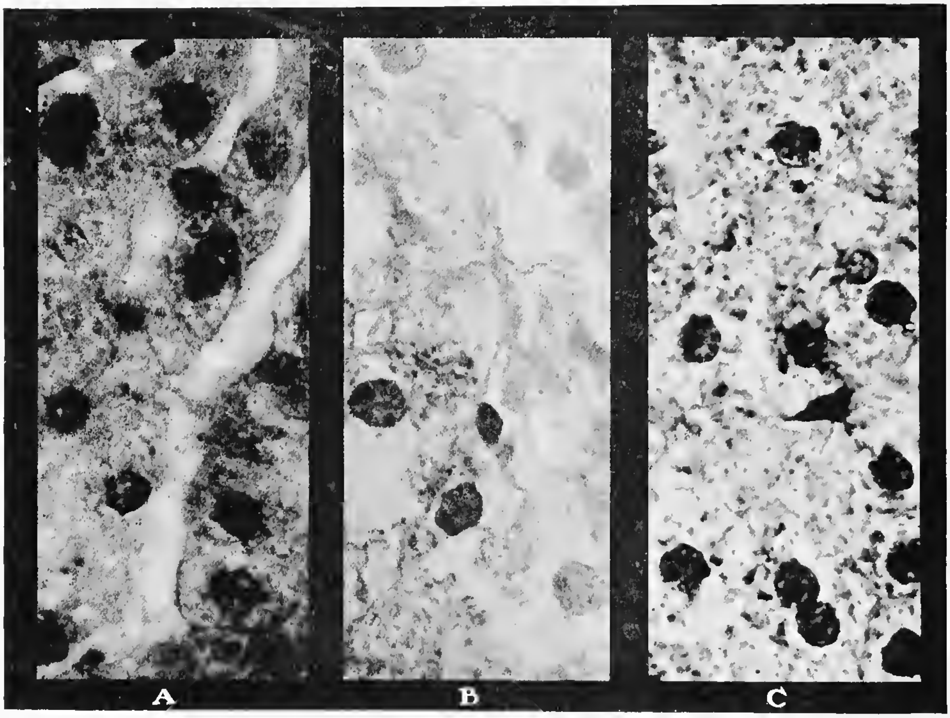


FIG. 97. Restorative Effect of Sleep in the Presence of Acidosis.

A, Section of normal liver.
B, Section of liver after the intravenous injection of hydrochloric acid.
C, Section of liver when the animal had had a prolonged period of sleep after the injection of hydrochloric acid.

(From photomicrographs, 1640.)

3. In every type of exhaustion changes in conductivity were observed, these changes in general corresponding with the histologic picture.

The conductivity changes in the liver are more marked and appear more promptly than the changes in the brain.

Why is as much change in electric conductance produced by mere quiescent insomnia, as by massive injury, overwhelming infection, intense emotion,

extreme exertion, etc.? On an electro-chemical basis this may possibly be explained by assuming that the weak electric impulses that perform mild work, and the strong impulses that perform intense work, are in each case flowing constantly in the same direction, and therefore the total transfer of electrolytes in each case obeys Faraday's law of electrolysis: *The mass of an electrolyte*

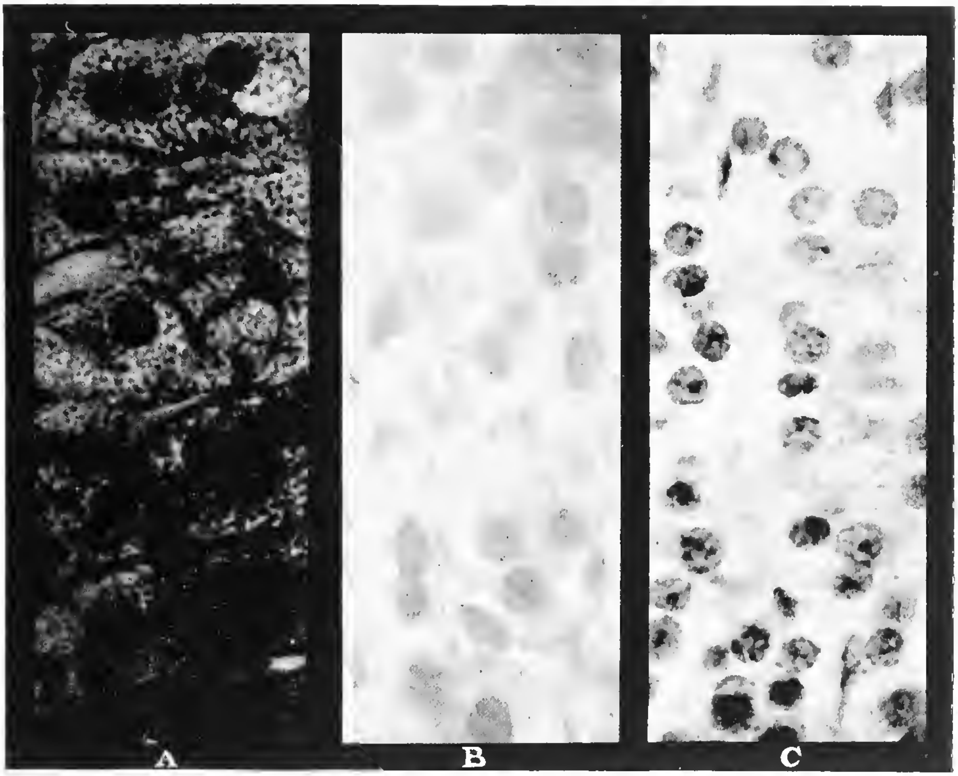


FIG. 98.—Restorative Effect of Sleep in the Presence of Acidosis.

A, Section of normal adrenal.
B, Section of adrenal after the intravenous injection of hydrochloric acid.
C, Section of adrenal when the animal had had a prolonged period of sleep after the injection of hydrochloric acid.

(From photomicrographs, 1640.)

set free by the passage of a current of electricity is directly proportional to the quantity of electricity which has passed through the electrolyte.

Glazebrook comments on this law as follows: 'It is a consequence of the first law that . . . a weak current flowing for a long time produces the same deposit as a stronger current flowing for a shorter time, provided the quantity

of electricity transferred is the same in the two cases.' Such a transfer of electrolytes when carried far enough may well destroy that state of electrical surface polarisation which Lillie states is a constant characteristic of living cells.[1]

If we consider the organism to be an electro-chemical mechanism, then the organism not only in exhaustion and shock but also in conscious normal activity, and in the antithesis of conscious activity—normal sleep—must obey the laws which govern the operation of electrical batteries. It is only during sleep that cells return to the normal—normal in appearance under the microscope, normal in electric conductivity, normal in function. In other words, it would appear possible that the phenomena and behaviour of man in the maintenance of normal consciousness, in exertion, in emotion, in fever, in injury, etc., obey Faraday's law.

Apparently, when there has accumulated within the cell a sufficient amount of acid to overcome the factors of safety, and every part of the cell has become acid, or when, through repeated discharges of energy, depolarisation has become complete, the difference in potential between interior and exterior is lost and the acidulated cell can do no work. The cell then is in the state of exhaustion.

From the foregoing considerations we conclude that, in exhaustion, two of the outstanding facts are intracellular acidosis and an abnormal redistribution of electrolytes, such as will produce depolarisation of the individual cells. These physico-chemical changes in the cells, which are believed to be disabling, have been demonstrated by two types of objective evidence — histologic changes, and changes in electric conductivity. Evidence along these lines, accumulated in our laboratory, has been given in Chapter I.

The interpretation toward which we are being led seems to lie in the domain of physics rather than of present-day physiology and pathology. In the following chapters, therefore, we shall develop the argument along physical lines.

[1] Lillie, R. S.: *Biol. Bull.*, 1917, xxxiii. 135-186.

CHAPTER IV

AN ELECTRO-CHEMICAL HYPOTHESIS AS TO THE MECHANISM OF EXHAUSTION

I. Is Exhaustion the Expression of the Failure of an Electro-Chemical Mechanism for the Transformation of Energy?

Biochemists have led the way to such a conception. Following their lead, and our laboratory and clinical findings, the following hypothesis as to the mechanism of exhaustion is proposed.

Let us suppose, as Mathews suggests, that the brain converts potential into electric energy, and that it is the driving force of this electric energy that enables man and animals to achieve adaptation to environment. If it were proven that the brain actually does fabricate electric energy as its chief energy-transforming function, then the translation of this electric energy into the driving force which operates the body would not be difficult to follow. Let us test this hypothesis as far as our limited knowledge will permit, and see how far it will harmonise laboratory and clinical data. In support of the electro-chemical hypothesis are the following facts :—

1. Electric stimulation of the controlling nerve supply of the various voluntary muscles and of the various glands of the body makes these muscles and these glands do what the brain makes them do.

2. Stimulation of the motor area of the cortex of the brain causes muscular activity resembling everyday voluntary activities, such as closing the hand, bending the wrist, the elbow, the ankle, the knee or the thigh, chewing, turning the head, turning the eyes, puckering the lips, increasing the respiration, etc.

3. Gotch and Horsley [1] have shown that during electric stimulation of the cortex, causing muscular action of the leg, a sustained electro-motive force was demonstrated in the spinal cord during the continuance of the stimulation. Not only did they demonstrate an electric wave, but they were able to pick out the conduction paths in the spinal cord over which this wave travelled. The current found its way along the intricate pathway from cortex to muscles, passing over the various synapses with accuracy.

[1] Gotch, F., and Horsley, V.: *Phil. Trans.*, 1891, clxxxii. 267-526.

These facts seem to indicate that electricity is adapted to the organism ; and that the organism is adapted to electricity.

The severing of the nerve connection between the brain and a muscle leads not only to paralysis, but to atrophy of the muscle ; but if the muscle be made to contract at certain intervals by electric stimulation, no atrophy of the muscle follows. Electricity does for the muscle, as far as its function and nutrition are concerned, what the brain does for it. Therefore, electricity is adapted to the muscle and the muscle is adapted to electricity.

4. Piper [1] showed that sound waves originate an electric current in the auditory nerve of fish. Electric stimulation of the auditory apparatus causes sound. Electric stimulation of the optic nerve produces the sensation of light. Einthoven and Jolly [2] confirmed the discovery made by Holmgren in 1866, that when light falls on the retina an electric current is produced in the optic nerve. That is to say, light produces electricity in the optic nerve ; electric stimulation of the optic nerve produces light. The observation of Einthoven and Jolly is highly important in another respect. The nerve mechanism of the eye is a projection of a part of the brain tissue on a stalk through an opening in the skull. Therefore, if this part of the brain mechanism is electro-chemical, we may suppose that so also are the olfactory centres, the centres of common sensation, and other parts of the brain.

5. Excessive electric stimulation of glands, such as the salivary glands, causes intracellular changes analogous to the changes present in the brain-cells in exhaustion (Howell).[3]

6. Excessive electric stimulation of the afferent nerves to the brain, or excessive electric stimulation of the brain itself, causes exhaustion of the brain-cells, just as excessive normal stimuli cause exhaustion. Protracted light electric stimulation produces brain-cell changes seemingly identical with the changes produced by stronger stimulation for shorter periods, *i.e.* they apparently obey Faraday's law.

7. Howell [4] states that when nerves of one kind are sutured to nerves of another kind, the reaction is determined by the end mechanism, and he states further that efferent nerves are like electric wires—the effect of their stimulation depends on the mechanisms found at their ends. The same electricity going over like wires may cause the explosion of powder, operate an arc light, turn a wheel, or do electroplating. It has been said that if we could attach the optic nerve to the ear and the auditory nerve to the retina, we should see thunder and hear lightning.

We have now reviewed some of the normal functions of the body which

[1] Piper, H., *vide* Starling, E. H. : *Principles of Human Physiology*, 1915, p. 603.

[2] Einthoven, W., and Jolly, W. A. : *Quart. J. Exper. Physiol.*, 1908, i. 373-416.

[3] Howell, W. H. : *Text-Book of Physiology*, 1913, p. 751.

[4] Howell, W. H. : *ibid.*, p. 80.

are controlled by electricity precisely as they are controlled by nerve action. Is it probable that two things which are proved equal to the same thing, *i.e.* forces which are so perfectly interchangeable, so capable of producing the same end-effect, with the same equipment, in a thousand reactions, are unlike each other in their essential characteristics ?

8. Is there direct evidence that potential energy is transformed into electric energy by the brain-cells ?

As the result of the passage of the normal action current down a nerve fibre, Tashiro [1] has shown that much carbon dioxid is given off and much oxygen is consumed. That is to say, the nerve fibre transforms energy. Tashiro has shown also that when a nerve is stimulated by electricity, carbon dioxid is given off, and oxygen is consumed in just the same way ; but in either case, *no heat is produced*. A. V. Hill,[2] through exhaustive studies, confirmed Tashiro's findings as to the absence of heat. Benedict also has demonstrated that no heat results from brain activity.

9. During the passage of a stimulus initiated by normal brain action, there is a negative variation. Gotch and Horsley [3] demonstrated a persistent negative variation in the cord during electric stimulation of the Rolandic area. That is to say, the passage of an action current over a nerve, whether that action current be the result of electric stimulation or of environmental stimulation, produces identical phenomena in the nerve over which it passes.

In the case of the action current in a nerve, there is no motion ; no heat is produced, no light is produced ; therefore, the nerve during stimulation probably produces electric energy. The axis cylinder is a part of the nerve-cell. If one part of the nerve-cell (axis cylinder) transforms potential energy into electric energy, then we conclude that the remainder of the nerve-cell may transform potential energy into electric energy without passing through the form of heat—as is known to be the case in the electric fish. The presumption, then, is strong, if not conclusive, that nerve-cells transform potential into electric energy.

10. Among the difficulties in the way of the acceptance of the theory, first proposed by Du Bois-Reymond, that the action current and electricity are identical, is the fact that the speed of the action current is low as compared with the high speed of the free electric current passing through ionised air, or through good conductors. Here, again, we turn to the principle of adaptation for aid in harmonising this difference. We must see what evidence there is that nerve tissue has been evolved to slow the electric current to a biologically workable speed, for, obviously, the instantaneous action of electric currents,

[1] Tashiro, S.: *Am. J. Physiol.*, 1913, xxxii. 107-136.

[2] Hill, A. V.: *J. Physiol.*, 1912, xliii. 433-440.

[3] Gotch, F., and Horsley, V.: *loc. cit.*

travelling at the rate of free electricity in the air, would rattle the skeleton of man to pieces, and make his movements biologically impracticable. If there is in the nerve-muscular system a mechanism which slows down the passage of electricity, then the speed of electric stimulation would approximate that of normal brain action. We have seen that on electric stimulation of the cortex of the brain in man and animals, the time that elapses between the electric stimulation of the cortex and the muscular response is approximately the same as that consumed in a voluntary response. The voluntary stimulus and the electric stimulus start at approximately the same point and arrive at their goal in approximately the same time. Is not each responding alike to a mechanism evolved to control the speed of the electric current to a biologic rate? Is there other evidence that a retarding mechanism exists?

Nernst [1] has supposed that the electrolytes in the axis cylinder lie within membranes which are impermeable to certain ions. When an electric current is passed through a nerve, it is conveyed by the dissociated electrolytes, causing an accumulation of positive ions at one point and of negative ions at another. When the concentration reaches a certain point, excitation occurs. A. V. Hill [2] supports Nernst's general theory, and has treated the subject mathematically. McClendon, Bayliss, Lillie, and others take a similar view. Such a mechanism would be competent to control the speed of conduction. The synapses also diminish the speed. MacCallum, by micro-chemical methods, showed that because it contains a greater concentration of electrolytes, the axis cylinder is a better conductor than the medullary sheath. Crehore and Williams [3] have put forward strong evidence in favour of the identity of the action current and electricity, and were able, by calculation, to predict the rate of conductance of artificial nerves. Meyer [4] found that alteration in the concentration of electrolytes in the sea water, in which the nerve of a marine animal was suspended, altered equally the rate of *electric conductivity of the water and the rate of nerve conduction*. Apparently nerves are core conductors.

Further evidence of the identity of nerve impulse and electricity is found in the fact that a rise of one degree of temperature increases electric conductivity 2·5 per cent. This should be compared with the finding that, with each degree of rise in temperature, the metabolism of the organism is increased 10 per cent. If electricity is the motive force of metabolism, then whatever facilitates its conductance (*e.g.* heat, iodin) increases metabolism.

11. Our electric conductivity studies have shown that, *excepting in the fetus*, the specific conductivity of the cerebrum is always higher than that

[1] Nernst, W.: *Arch. f. d. Ges. Physiol.*, 1908, cxxii. 275-314.

[2] Hill, A. V.: *J. Physiol*, 1910, xl. 190-224.

[3] Crehore, A. C., and Williams, H. B.: *Proc. Soc. Exp. Biol. and Med.*, 1913, xi. 58.

[4] Meyer, H. H.: *Munch. Med. Wchnschr.*, 1909, lvi. 1577-1580.

of the cerebellum, and that the conductivity of the voluntary muscles is the highest of any of the tissues of the body. Therefore, if the brain-cells create electricity, it would flow out through the cortex, and thus, we may suppose, activate the motor area, passing thence along the lines of least resistance to the voluntary muscles. Striking confirmation of this assumption is found in the fact that in the fetus the relative conductivities of the cerebrum

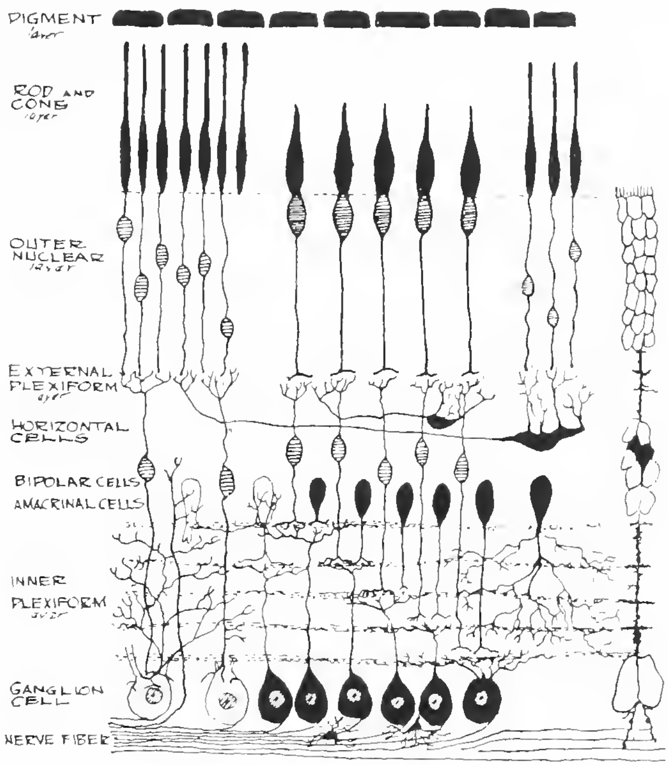


Fig. 99.—Structure of the Human Retina.
Adapted from Howell, *Text-Book of Physiology*, 1913, p. 354.

and of the cerebellum are reversed. That is, before conscious life begins, while the motor areas are silent, the current following the lines of least resistance activates only those centres which govern vegetative activity (see Fig. 84). During intense excitation caused by physical injury, emotion, infection, strychnin convulsions, and the injection of adrenalin, the conductivity of the brain is increased. In the stage of exhaustion the conductivity is decreased.

12. All living matter shows electric energy; dead organic matter shows none. It is electric energy that organises cells—*e.g.* electric treatment prevents

disorganisation of the muscle when its nerve supply has been divided; if the eyes of puppies are permanently closed by operation at birth, the corresponding parts of the brain-cells do not develop.

13. Burdon-Sanderson[1] first demonstrated that motor plants, such as Venus' Fly-Trap and the Sensitive Plant, show electric variations during their activity. Waller[2] extended these observations, and designated the electric variations 'blaze currents of action.' Bose[3] has found evidence of the identity

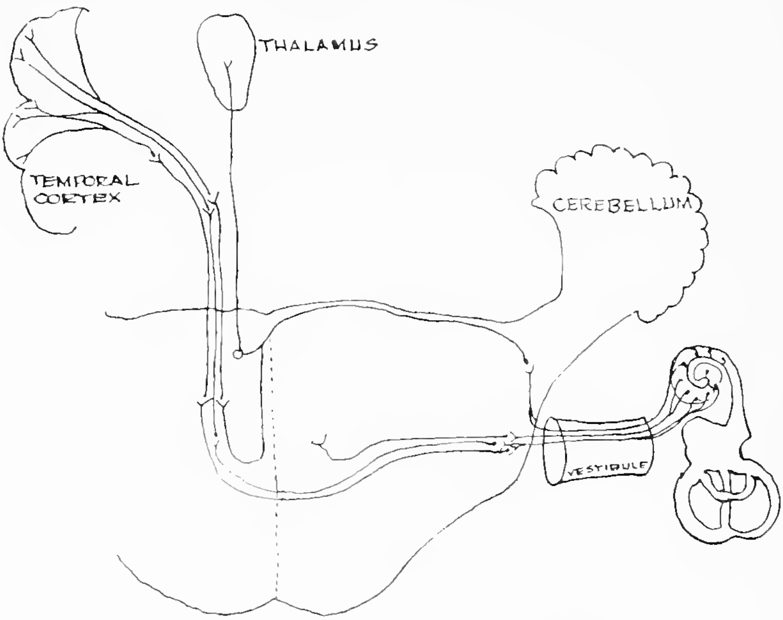


FIG. 100.—Connections of the Auditory Nerve.
Adapted from Piersol, *Human Anatomy*, 1907, p. 1258.

of vegetable and animal activity, demonstrating that each results from the operation of an electro-chemical mechanism.

14. When we consider the structure of the receptor mechanisms of the eye (Fig. 99), of the ear (Fig. 100), of the taste bulbs, of the touch corpuscles; the nerve endings in muscles and glands (Fig. 101); the fact that nerve processes do not meet, but communicate through synapses (Fig. 102);—what agency but electricity could traverse and activate such a mechanism (Fig. 103)? It would seem that chemical action could no more operate this infinite net-

[1] Burdon-Sanderson, J. S.: *Phil. Trans.*, 1882, i. 1-55; 1888, ii. 179 (B), 417-449.
[2] Waller, A. D.: *Report Brit. Ass. Adv. Sc.*, 1913, Lond.; 1914, pp. 241-258.
[3] Bose, J. C.: *Plant Response as a Means of Physiological Investigation*, 1906.

work of conducting wires of microscopic size than chemical processes could travel in free space to activate the wireless telephone or telegraph ; or take the place of the wireless control of the locomotion of a boat at a distance. Even a glance at the finer structure of the sense organs and the brain will tell us how difficult it would be for chemical processes to follow microscopic interlacings in a semi-fluid medium without spreading ; how difficult it would be for chemical action to leap across synapses, and traverse the infinitesimal, interwoven wires of the brain. On the other hand, electricity shows that it is

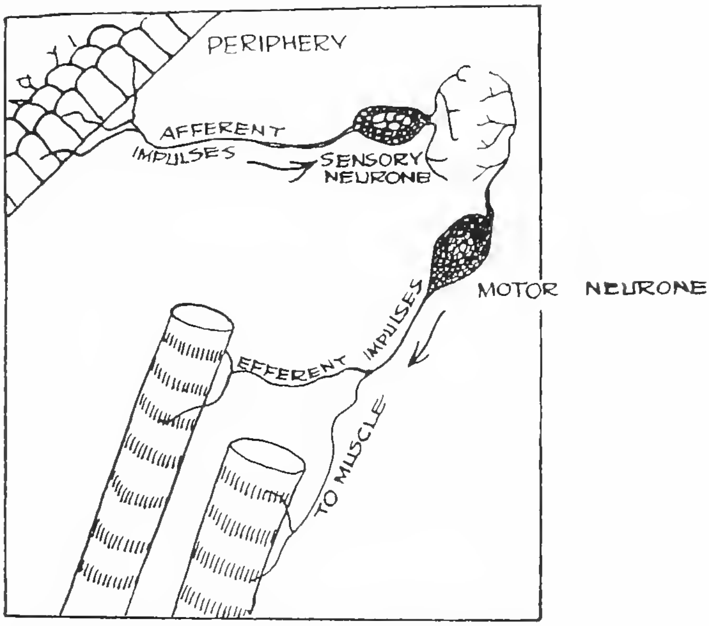


Fig. 101.—Fundamental Units of the Nervous System. Adapted from Piersol, *Human Anatomy*, 1907, p. 996.

qualified to do just this ; it has done just this, and may be seen in the act of doing just this in every form of life. It is electricity, not chemical action, that operates the telephone, the telegraph, the wireless. A savage would probably regard these as operating spiritually or by a vital action.

The mere fact that the brain has no insulated nerve paths may suggest infinite confusion in the passage of electric currents ; but this apparent difficulty lends itself to a harmonising interpretation, viz. that the electric current elects pathways facilitated by ontogeny and by phylogeny, these providing the means for a vast variety of response. We may regard the free fibrillar endings in the brain as receptors for electricity, just as the free endings

of the optic nerve are receptors for light. Analogous to these receptor mechanisms are man-made mechanisms—the receiving instrument of the wireless telegraph, the 'selenium eye' of Hammond's artificial dog, the audion.

15. Anesthetics diminish the power of the brain and of the muscles to do work. Our electric conductivity measurements show that ether diminishes the conductivity of the cerebellum. Lillie[1] has pointed out that anesthetics interfere with the increase of permeability of the semipermeable membranes to the passage of ions. Anesthetics diminish the physiologic activity and the electric phenomena of plants.

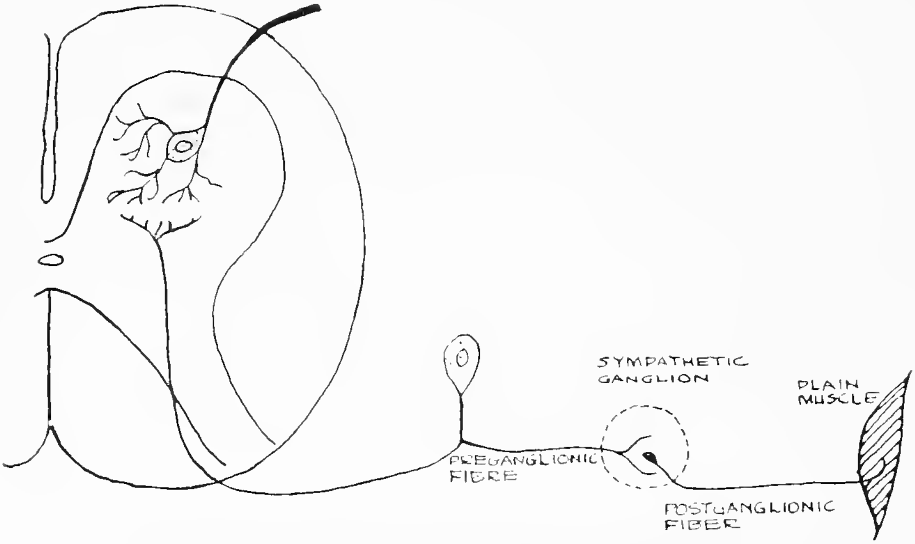


FIG. 102.—Schema Illustrating the Autonomic Paths of Action. Adapted from Howell, *Text-Book of Physiology*, 1913, pp. 140, 247.

16. The process of oxidation, which is the only means by which body-energy is secured, is an electric process; it is transference of negative and positive charges. The basic property of protoplasm, viz. irritability, is shown by biochemists to be due to changes in permeability to the passage of ions through the semipermeable membranes of cells. Cells are the units which generate the power of the body—cells are electric batteries (Mathews, Lillie). Electricity is concerned in the changes in permeability of the semipermeable membranes of cells and in the surface tension phenomena; it is manifested by the electrolytes and colloids found everywhere in the cells. The cells are constructed as if for the creation of electricity, or for being operated by electricity. It would be as difficult to show that a wireless apparatus or the telegraph or the

[1] Lillie, R. S.: *Biol. Bull.*, 1909, xvii. 188-208.

telephone is designed to operate as a purely chemical machine, or to be operated by some mystic force, as to show that the organism, the basis of which is the cell, is so operated. The smaller the cells, the greater the ratio of the surface area to volume; the greater the surface area, the greater the capacity to carry an electric charge. The brain-cells are exceedingly small, and are ideally adapted to enable the brain to bear maximum electric charges. Whenever the body of a cell and its nucleus have lost their difference in potential, as by acidity, or by penetration of the nuclear membrane, etc., then the cell

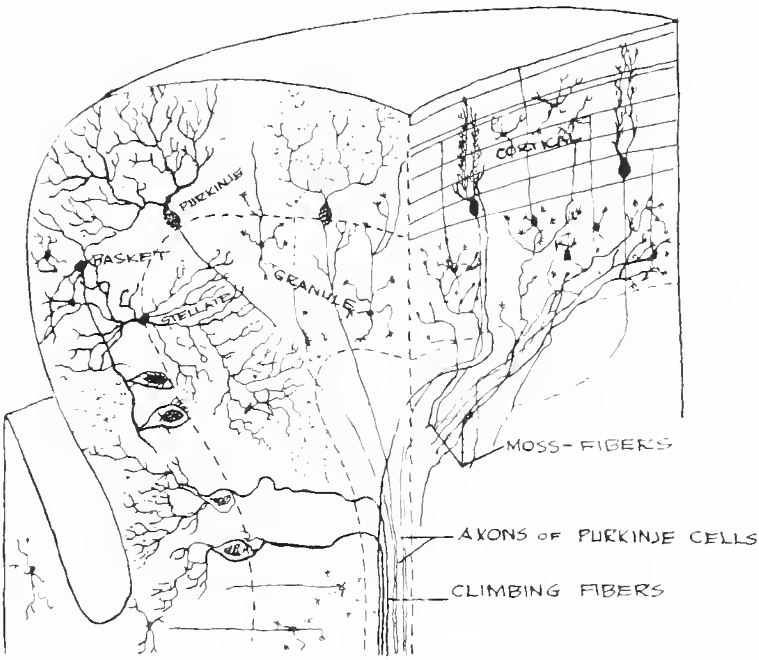


FIG. 103.—Relations of Nerve-Cells and Fibres of Cerebellar Cortex. Redrawn from Piersol, *Human Anatomy*, 1907, p. 1092.

soon loses its ability to do work, just as in the electric battery, if there is no difference in potential, there is no electro-motive force—no power to do work.

17. Evidence of the identity of the action current and electricity is not confined to laboratory and clinical observations; there is evidence in natural history, also. There is no more fallacious evidence, if wrong, and no more certain evidence, if right, than that secured by reasoning from the criteria of the biologic struggle and survival of species. On the assumption that such evidence rests on a sound basis, we shall base the following argument on the premise that the outward form and the inner processes of man and of animals

are the result of an age-long struggle for survival. The presence of powerful horns in one animal presupposes a strong muscular enemy. The presence of a keen sense of smell presupposes odor in an antagonist or in the animal sought for food. The presence of the skunk's repellent odor presupposes the keen hostile scent of hunting enemies. The presence of the barbs of the porcupine

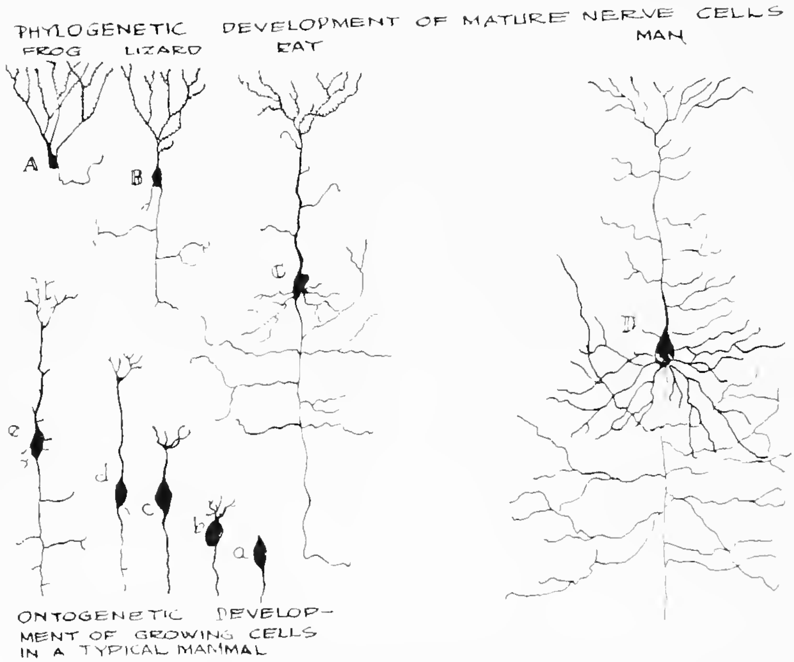


FIG. 104.—Phylogenetic and Ontogenetic Development of Mature Nerve-Cells.

'The number of processes, particularly the dendrite processes, is much greater in the cortical cells of the higher animals; or to put this fact in another way, the number of cells in the cortex of the higher animals is much less for an area of the same size than in lower animals. The amount of in-between substance or the richness of the network of processes is increased. This anatomical fact would indicate that the greater mental activity in the higher animals is dependent, in part, upon the richer interconnection of the nerve-cells.' Redrawn from Howell, *Text-Book of Physiology*, 1913, pp. 185, 186-187.

presupposes the soft, vulnerable nose of the carnivorous pursuer. The presence of color or of form obliteration presupposes the sharp eye of an enemy. The presence of fleet limbs presupposes an adversary of lithe muscles. In the long list of defence mechanisms, whether active or passive, the defence relates to some force used by the enemy. The means of defence is not created anew; in each case it is a modification of pre-existing tissue. Thus the horns, the barbs, the carapace, are modifications of the skin; poison and odor are produced by

modified glands. Just as the fleet limbs of pursuit resulted in the fleeter limbs of escape and stronger horns of defence, so the sharp tooth was met by the hardened carapace, the keen nose by the repellent odor, the electrically driven jaws by the higher electrical charge of the fish and eel.

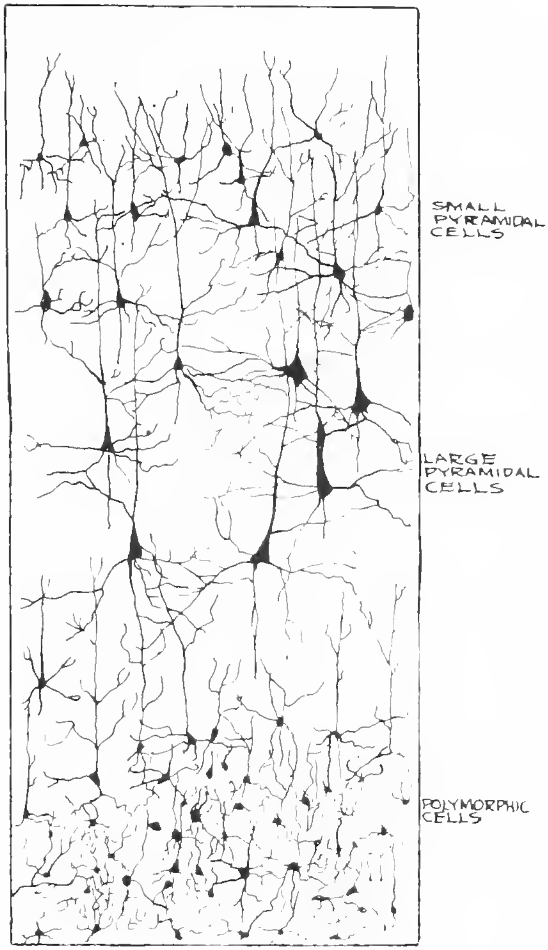


Fig. 105.—Nerve-Cells of Cerebral Cortex.
Redrawn from Piersol, *Human Anatomy*, 1907, p. 1178.

How came some animals to evolve an electric defence? May we not infer that it was due to the fact that a stronger electric charge would neutralise the weaker electric stimulus of the muscles that would attack the electric fish? For in the pursuing animal, we suppose that the electro-chemical mechanism

is slowed down adaptively to permit orientation and a rate of speed that will not shake the body to pieces, while the electric fish has the advantage of a free electric charge, which is about a million times swifter in its release than is the evolved bioelectric charge of the attacking animal. The higher potency of the electric charge of the defending animal would instantly overcome and disorganise the lighter and biologically slow electric charge operating the muscles of the pursuing enemy. Dahlgren[1] has shown that the electric fish does not store electricity, but that the electricity is fabricated instantaneously by the cells. The evolution of large numbers of cells in series gives this great electric power. Were the muscle mechanism of animals not electro-chemical, would there be any more likelihood that there would have been developed animals with electric defence, than that there would have been developed fleet muscles for escaping if there had been no fleet muscles for pursuit; or that the defence of odor would have been developed, had there not been an hostile nose?

If one function of the brain be the transformation of potential into kinetic energy, in the form of electric energy, then it should not be difficult to suggest the method and the mechanism by which this electric energy drives the body. One would suppose that the brain-cells, like the electric cells of the electric fish, are charged with highly evolved, labile energy ready to be instantly transformed into electric energy on the arrival of the adequate stimulus. The electric charge thus set free within the operating mechanism has a free run among the various parts of the brain and down the nerve fibres to the numerous muscles and glands. The receptor mechanisms—the touch and pain receptors, the receptors for waves of light, the receptors for waves of sound, the chemical receptors for apprehending taste and smell and foreign proteins, the receptors for apprehending changes in acidity, the thermal receptors for appraising external heat and cold, the receptors for apprehending distention and obstruction of the viscera,—all these receptors when adequately stimulated would activate the mechanisms that give response, the excessive activation of which would lead to exhaustion. Thus, lying, sitting, standing, chills and fever, walking and jumping, playing and working, sighing and fighting, laughing and weeping, eating, sneezing, vomiting—all would be executed by means of the activation and inhibition of the electrically driven muscles, as long as there is life.

How easy it is to conceive that the work of the body can be accomplished through the operation of an internal electro-chemical mechanism, when the clumsy man-made electric battery can act as a substitute for the infinitely delicate, living, biologic, electric mechanism which has been evolved through æons—the highest achievement of infinite struggle and survival. That a

[1] Dahlgren, Ulric: Carnegie Institute, Washington, Publication No. 183.

crude, man-made electric method of stimulation can make the biologic electro-chemical mechanism do its work suggests that the biologic electric mechanism of animals was evolved to utilise electricity as its means of achieving adaptation.

From the foregoing considerations, we may infer that man is an electro-chemical mechanism: that within this mechanism the brain and nerve cells have been evolved in the age-long struggle for survival for the transformation of potential energy into electric energy: that the energy-transforming function of the brain-cells is so vital that the brain-cells are not hampered by the presence of lifeless, inert matter in the form of food; or in the form of elements which protect against acidosis or against want of oxygen; that the food and the protective mechanisms against acids are contained within the cells of other organs, especially the liver, which apparently holds fuel in loose chemical bonds just as the blood itself holds oxygen in loose chemical bonds. The acid by-products of the energy-transformation in the brain-cells are at once picked up by the buffer substances in the rich supply of blood and lymph, and in turn these substances are taken from the blood by the liver. In acidosis, we may suppose that the liver throws out glucose for the protection of the brain. In asphyxia, the anaerobic oxygen in glucose appears in the blood for the protection of the brain. When acidosis develops as a result of lack of oxygen, lack of food or water, overwhelming stimuli, excessive work, or lack of elimination of acid by-products, or any other causes such as anesthesia or the presence of cyanides, or when any other causes prevent the brain-cells from transforming potential into electric energy, then there is exhaustion. Exhaustion appears also when the mystic reversible process of sleep is wanting. Sleep is the daily restorer of the brain, hence restoration, like exhaustion, begins and ends in the cells.

II. An Electro-Chemical Interpretation of the Inceptive Stage of Primary Shock

In accordance with the conception that the phenomena of exhaustion are electro-chemical phenomena, the inceptive stage of primary shock may be interpreted as follows:—We may assume that an electro-chemical mechanism, such as the brain-cell, evolved so delicately as to be responsive to infinitesimal physical forces, such as a ray of light falling upon the retina, is a mechanism that may be easily injured. Just as the direct rays of the sun injure the photo-electro-chemical mechanism of the eye and cause impairment or loss of sight, so we may suppose the brain-cell can be functionally impaired or broken down by the excessively violent stimuli of trauma. The mechanism of sight is evolved too delicately to endure the direct rays of the sun; if it

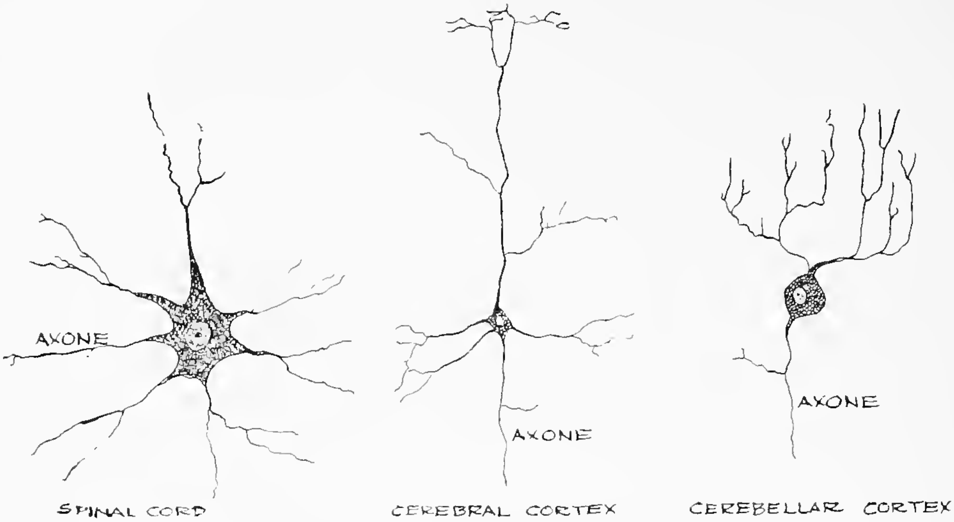


FIG. 106.—Multipolar Nerve-Cells.
Redrawn from Piersol, *Human Anatomy*, 1907, p. 1000.

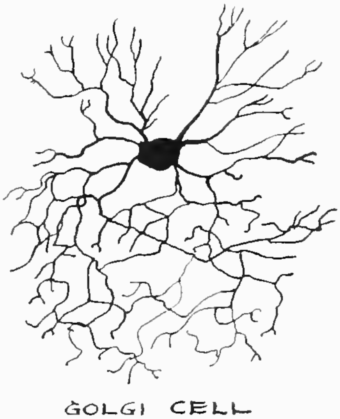


FIG. 107.—Golgi Cell (second type), 'characterised by the fact that the axon process instead of forming a nerve fibre splits into a great number of branches within the grey matter. Assuming that in such cells the distinction between the axon and the dendrites is well made and that as in the other type the dendrites form the receiving and the axon the discharging apparatus, these cells would seem to have a distributive function. The impulse that they receive may be transmitted to one or many neurons.' Redrawn from Howell, *Text-Book of Physiology*, 1913, pp. 132-133.

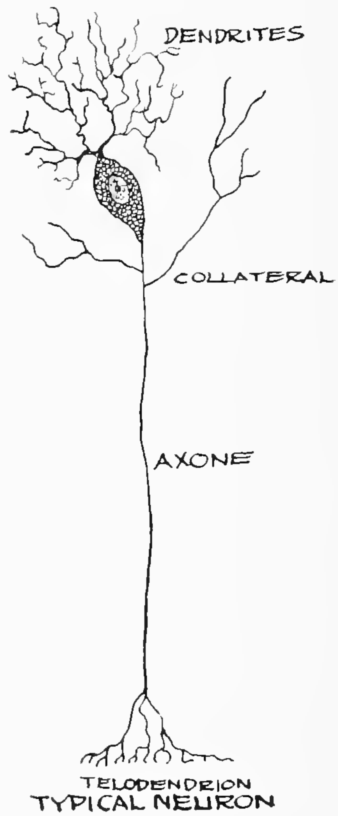


FIG. 108.—Diagram of a Typical Neuron. Redrawn from Piersol, *Human Anatomy*, 1907, p. 997.

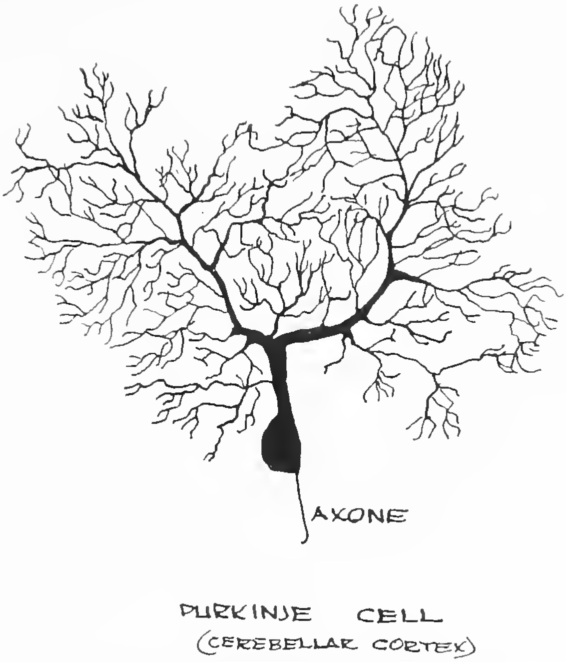


Fig. 109.—Schematic Drawing of a Purkinje Cell Illustrating the Arboreal Arrangement of the Dendrites.

Adapted from Piersol, *Human Anatomy*, 1907, iv. 1091.

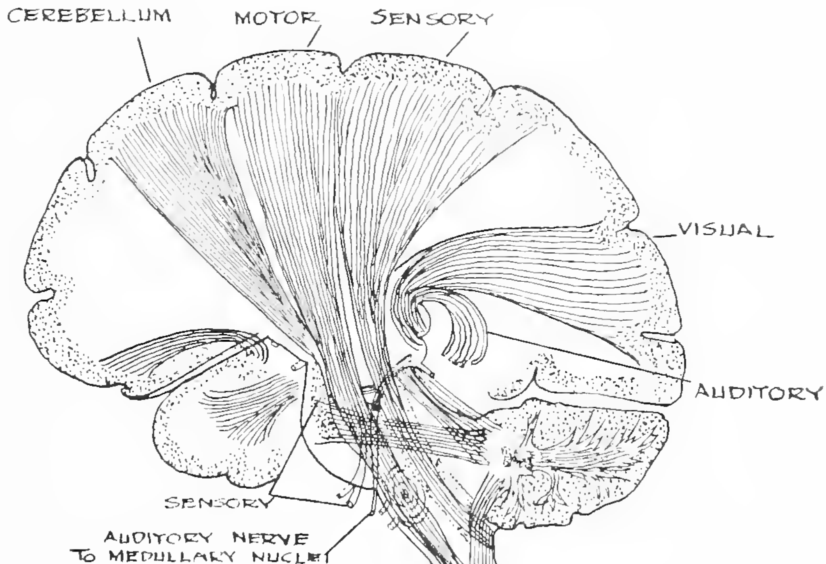


Fig. 110.—Schematic Drawing Showing the Connection of the Projection Tracts of the Cerebrum with the Lower Nerve Centres.

Adapted from Howell, *Text-Book of Physiology*, 1913, p. 183, and Gray's *Anatomy*, 1913, p. 956.

were evolved to endure the direct rays of the sun it would probably be irresponsive to ordinary light. By analogy, we may reason that if the nerve receptors of common sensation were so obtuse as to respond normally to a compound fracture of the thigh, they would fail to record the everyday lighter contacts. The sensory mechanism is adapted to the lesser environmental contacts—not to fractured thighs or evulsions of limbs—just as the eye is

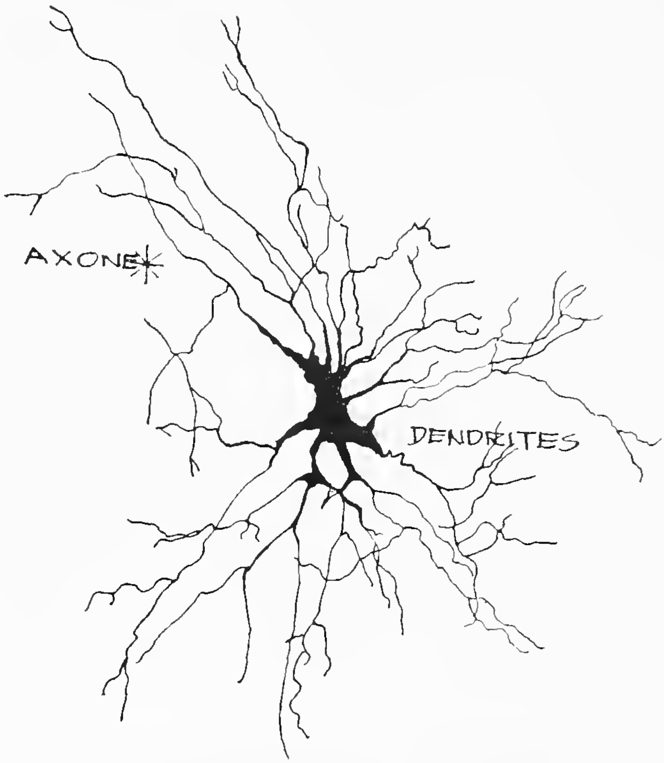


FIG. 111.—Motor Cell, Anterior Horn of Gray Matter of Cord. Redrawn from Howell, *Text-Book of Physiology*, 1913, p. 129.

attuned to ordinary light, not to the sun itself. If this reasoning be correct, then stimuli of excessive intensity would cause an *immediate* impairment of the power of the brain-cell to do work.

If the brain-cells suffer an immediate internal injury as the result of excessive trauma of sensitive tissue, then one would expect to find immediate evidence of that impairment in altered conductivity, and in change in the reserve alkalinity in the blood coming from the brain. Our electric conductivity studies have shown that in the inceptive stage of shock there is an

early increase in the alkalinity of the blood coming from the brain, and an immediate *increased* conductivity of the brain-cells followed quickly by a decreased conductivity (see Figs. 83 and 88-90). These findings supply the evidence that the brain suffers an immediate impairment of function independent of a decrease in blood-pressure changes. These experiments may be open to other interpretation; but they indicate an immediate impairment of the function of the brain before the blood-pressure falls. This inceptive stage is indicated also by the early stage of hyperchromatism demonstrated in our histologic studies.

From these experiments it appears, with query as noted, that intense traumatic stimuli cause an immediate injury to the brain-cell analogous to the injury caused by direct sunlight upon the photo-electro-chemical mechanism of the eye. Therefore, in overwhelming traumatic psychic or toxic stimuli, the loss of the power to fabricate heat, the loss of muscular power, the loss of mental power, would be a natural sequence—an end effect.

These experiments apparently establish a continuity of disability from the inception of the injury through the period in which the factors of safety are consumed until finally the resulting low blood-pressure with its injuring cycle of events causes the ultimate breakdown of the mechanism. If our interpretation of these experiments is correct, then the missing link between injury and the inception of primary shock and secondary shock is supplied by the extension of the kinetic theory to include the electro-chemical conception as stated.

CHAPTER V

A THEORETICAL CONSIDERATION OF THE MECHANISM OF RESTORATION

I. Histologic Evidence

As seen under the microscope, the first physical change in the brain-cell which results from intense stimulation from any cause, is *hyperchromatism.*

2. *Hyperchromatism* is always followed by *chromatolysis.*

3. *Chromatolysis* is attended by increasing *edema.*

4. *Edema*, if too great, causes the covering membrane of the cell to *rupture.*

5. *Rupture* of the covering membrane of the cell is soon followed by rupture of the covering membrane of the *nucleus.*

6. *Nuclear function* of the brain-cell is lost when its membrane ruptures.

7. *Rupture* of the nuclear membrane, if extensive, ends permanently the activity of the cell—causes its *death.*

8. *Death* of the brain-cell, then, is one of the final *sequelæ* of extreme *exhaustion.*

9. *Exhaustion* of the cell to a less degree than to the death point, is followed by *restoration.*

10. *Restoration* takes place chiefly, perhaps only, during *sleep.*

11. *Sleep* is the antithesis of *activity*, and no brain-cell can work and live without *sleep*; sleep restores that property of the cell by means of which the cell is enabled to show a differential stain, by means of which presumably a difference of potential is maintained, making possible *consciousness.*

12. *Consciousness* is the active phase—*sleep* the negative phase of the brain-cell.

II. Electro-Chemical Bases of Restoration

1. Assuming that cells are electric batteries, the maintenance of whose electro-motive force depends upon the semipermeability of the plasma membrane, and that electric batteries, during action, undergo a continuous passage of ions in such a way as to deplete the reserve of chemical energy and

eventually destroy the electro-motive force or polarisation of the battery, it may be inferred that sleep marks the reverse process of repolarisation, or reaccumulation of electrolytes so separated by a semipermeable membrane as to give rise to electro-motive force.

2. *Polarisation and depolarisation*—*i.e.* the periods of activity and of sleep—like the periods of activity and of recharge in a battery, if its full efficiency is to be maintained—are approximately equal.

3. If the period of work—*i.e.* if the passage of electric current is short, as in the heart-beat—then during that time the degree of depolarisation is *proportionately small.*

4. The small degree of depolarisation which results from a single heart-beat requires a proportionately short time for repolarisation or sleep—*i.e.* the pause in the heart cycle may be regarded as its period of sleep.

5. The heart, with its nerve mechanism, takes normally from seventy to ninety naps a minute, and thus is kept polarised or rested as it works.

6. We may suppose that the nerve-cells which operate the respiratory mechanism become polarised,or sleep, from sixteen to eighteen times per minute, and the respiratory mechanism is kept polarised or rested as it operates.

7. The salivary glands, the intestinal nerve muscle mechanism, the digestive glands, etc., we may suppose, have alternating periods of *work and depolarisation*, and of *sleep and repolarisation*. Regarded superficially, the functions of respiration, of circulation, of digestion, carry on as if they never rested, never slept; but their sum-total of short periods of sleep is quite as large as the total period of sleep of that part of the brain whose work creates consciousness, and therefore spends no more time in sleep, but sleeps more conspicuously.

8. As for the portion of the brain which governs conscious activity, the periods of work, and therefore of depolarisation of the cells that supply the electric power for consciousness, for emotion, and muscular action, are longer than the periods of work of the heart, of the respiratory or of the digestive mechanism. For man, the period of sleep of the higher centres supplies an opportune means of taking advantage of the protection of night. The option of evolution apparently has been to run the organism on long shifts or shorter ones. If the brain operated in accordance with the time-table of the heart, man would become unconscious and would fall from seventy to eighty times a minute.

In the higher animals the established longer periods of work and of restoration for the central nervous system are adaptive, just as the short periods of work and of sleep for the heart and for the respiratory mechanism are adaptive. In other words, according as the central nervous system took advantage of light or of darkness for securing food, it took advantage of corresponding

periods of darkness or of light for sleep; while the heart, on the other hand, is compelled to work and to sleep at short intervals in order that the flow of blood may not be interrupted. It would appear, therefore, that the various animals as a whole and their several working parts have been adapted each to the most advantageous rhythm of alternating work and rest.

9. If the changes in the nerve-cells seen in fatigue from various kinds of work and from prolonged enforced consciousness are identical in appearance; if these physical changes are restored only during sleep; and if the degree of cell change varies with the amount of work done at a stretch without sleep—that is, with the amount of electric energy that has originated in or traversed a given cell—then it would require more time and deeper sleep to restore the electrical balance of the cell after prolonged heavy muscular exertion than after a day of restful quiet. And this is demonstrated by experience. It would appear that the degree of exhaustion equals the protraction of consciousness multiplied by its intensity.

10. As a corollary, we also know by common experience, as well as by experimentation, that the degree of restoration accomplished by a given period of sleep is proportional to the depth of sleep. For example, when a civilian from a comfortable environment enters the army and is obliged to sleep on rough, uneven ground, in cold and wet weather, in apprehension of the enemy, though his period of sleep may be long, its depth is apt to be shallow, and consequently his restoration is incomplete.

11. Sleep, being a negative phase, cannot be *compelled*. Consciousness, being a positive phase, can be *compelled—even unto death*. Normal man cannot sleep unto death; he can sleep only to restoration—no more.

12. Consciousness is more controllable than sleep; hence it follows that if the daily restoration be incomplete because of cold and wet, and noise and danger and apprehension, and the want of a comfortable place in which to lie down, there will develop a daily, weekly, monthly deficit of restoring polarisation—restoring sleep. Our experiments were not required to prove this: the proof is at hand and is common knowledge; for after a period of active duty in trenches, after a period of business or professional worries, of active, social life, when the heckled soldier gets back to a comfortable, quiet billet, or when the strenuous civilian goes aboard ship for a pleasant voyage, there follow long periods of sleep. After reaching the hospital, soldiers often slept continuously for even two days.

Not only is there evidence of the deficit of sleep in the normal stress of activity; but in disease also it is evidenced by increased sleep after the break of an acute fever and after the excision of the thyroid in exophthalmic goiter. The point to be remembered is that the hyperactivating stimulus of the day in the form of an emotion *prevents* deep sleep at night.

13. It is of significance that the brain and the voluntary muscles produce about 50 per cent. of the metabolism of the body; for if it be true that only the brain and the voluntary muscular system sleep for one long period each day, then during sleep the metabolism of the body could not be depressed more than 50 per cent. This point is supported by calorimetric studies made by Benedict and Milner.[1] These considerations support the view that the various parts of the body sleep at such intervals as are best for the organism as a whole. Apparently all active cells sleep, although by common usage the term sleep is applied only to the central nervous system, in its relation to the state of consciousness.

14. There is much evidence that if the by-products of strenuous work are left in the cells and remain too long unrelieved by sleep, there develops a gradually increasing impairment of the mechanism itself. In war this impairment is seen in war neurasthenia, in war neurosis; in civilian life it is seen in the overworked, ambitious pupil, in the over-driven, professional man, in the worried business man, in the anxious mother, attending a sick child or enduring a family disgrace.

15. It is suggestive that the conductivity of the brain is decreased by prolonged insomnia and restored by sleep (see Fig. 92).

16. In traumatic shock, in acute overwhelming *exertion*, in mixtures of various *kinetic drives*—the process may be so rapid, the pain so acute, the circumstances so compelling that the restoration of sleep cannot be invoked, and death occurs. There is no essential difference between the causation of the chronic and of the acute forms of exhaustion. In acute exhaustion, which can be relieved by several periods of prolonged sleep, an approximately normal state is re-established. In chronic exhaustion, longer periods of rest are required. In either case, in many instances permanent damage is done.

It is obvious that work and rest are parts of the same process within the cells of the organism. To gain an insight into the method by which the brain-cells are restored is to gain an insight into the mechanism by which the cell performs its work. The cell being an electric battery, and the action current being electric, variation in speed of work done must include a variation in something more than the rate of oxidation—there must be variation in the electric conductivity as well.

Osterhout has shown that iodin facilitates electric conductivity in *vegetable* cells. We have shown that iodin greatly increases the conductivity of *animal* cells, especially in the brain. The thyroid gland has been evolved to hoard and metabolise iodin (Marine),[2] and its secretion, therefore, would

[1] Benedict, F. G., and Milner, R. D.: *U.S. Dept. Agriculture, O.E.S. Bull.*, No. 175.

[2] Marine, D., and Williams, W. W.: *Arch. Int. Med.*, 1908, i. 349-384; Marine, D., and Lenhart, C. H.: *Arch. Int. Med.*, 1909, iv. 440-493.

facilitate the passage of electricity—hence the work of the cells. Oxidation —hence metabolism — is markedly controlled by adrenalin. Let us, then, consider the adrenals and the thyroid in the rôle of activators.

III. The Activators

THE ADRENALS AND THYROID

The Adrenals.—The adrenal glands are activators of the brain, and that their aid is promptly elicited when increased metabolism—increased work—is required, is shown by the fact that adrenalin alone produces nearly all the symptoms produced by the various causes of increased energy-transformation, such as emotion, exertion, injury, infection. That is, adrenalin causes increased metabolism, increased thyroid activity, increased blood-pressure, increased pulse, increased respiration, leucocytosis, increased sweating, dilation of the pupils, diversion of the blood to the surface, lowering of the threshold at the myo-neural junction.

Of no less significance are the facts that adrenalin causes hyperchromatism and later chromatolysis of the brain-cells, just as do emotion, injury, exertion, infection; that it causes an immediate increase in electric conductivity of the brain; and that when the adrenals are removed, the brain-cells rapidly degenerate, the animal rapidly loses the power to fabricate heat, and muscular and mental action; and death usually follows.

We conclude, therefore, that the brain is dependent on the adrenals, both for function and for survival. The adrenals may show enlargement in some chronic activations, such as infection, pregnancy, the rutting season, exophthalmic goiter. The adrenals, therefore, must be included among the means by which the organism is driven to exhaustion. It is, therefore, as important to consider the relation of the adrenals to restoration as their relation to exhaustion.

In our laboratory Mosiman found that adrenalin caused leucocytosis in rabbits. In the course of our researches in France at U. S. Base Hospital No. 4 (Lakeside Unit), Captains C. D. Christie and M. A. Blankenhorn found that leucocytosis was increased—even trebled—in the participants in a prize fight. Does leucocytosis appear in the activities that show an increased output of adrenalin? May leucocytosis be regarded as one of the adrenalin phenomena? Exophthalmic goiter cases show leucocytosis; the symptoms of exophthalmic goiter resemble those of adrenalin action. The symptoms both of excessive metabolism and of leucocytosis disappear after the removal of the excessive thyroid tissue.

Our studies of electric conductivity showed that adrenalin first increases

the conductivity of the brain, as in the inceptive stage of shock, and that the conductivity is then decreased, as in other forms of stimulation. If conductivity is related to stimulation, then an increase or decrease in conductivity would be associated with an increase or decrease in function, *i.e.* with activity or exhaustion. Our electric conductivity observations have indicated that in the inceptive stage of shock or exhaustion the conductivity of the brain is increased, while in every type of exhaustion studied, the conductivity of the brain was decreased when the state of exhaustion was established.

If the activation of the brain is a phenomenon of electric energy, then since electric energy depends upon oxidation, and oxidation in part at least is controlled by adrenalin, it obviously follows that excessive adrenalin would ultimately cause fatigue and decreased permeability.

It is not without interest to note, and perhaps it is significant, that convulsions frequently occur in the onset of acute infectious diseases in children, in which there is reason to believe that there is a free output of adrenalin, and a quick and powerful metabolic activation. This increased metabolic activity may be interpreted to mean an increased output of electricity, so great that the over-driven motor cortex in turn drives the organism to extensive muscular contractions—convulsions.

The experimental and clinical phenomena thus far placed in evidence are harmonised by the kinetic theory, and would seem to indicate that the body is driven by electricity, which is fabricated in the brain-cells with the aid of adrenalin. But we have seen no evidence that adrenalin covers more than the emergencies of moments and hours, or of days. We have seen adrenalin to be too evanescent, too volatile, to establish and to maintain evenly an increased receptivity, increased sensitiveness to response, an increased metabolism, both basic and adaptive, day and night, for weeks and months. We assume that the brain has no power within itself to do this, and that, therefore, prolonged activation is accomplished through the aid of some other organ. If electricity is the driving force of the organism, and if electric power is increased by increasing the conductance of the tissues over which it passes, it would follow that there must be in the body an organ which is capable of supplying to the blood for weeks and months a substance that is known to increase electric conductance—the blood in turn supplying this substance to the nervous system. The adaptive storage and discharge of such an agent would answer the theoretic need. As stated above, Osterhout has shown that iodin increases electric conductance in vegetable tissue, and our researches have shown that the conductivity of the brain, of the liver, of the muscles, of the spinal fluid, of the adrenals, of the heart, of the lungs, is increased by iodoform.

The Thyroid.—Now the function of the thyroid is that of seizing and storing

iodin and fabricating it into an iodin protein adapted to the needs of the organism. We have demonstrated in our laboratory, and surgeons are familiar with the fact, that iodin poisoning causes symptoms identical with the symptoms of acute infection. In iodoform poisoning we found brain-cell changes similar to those produced by exertion, emotion, infection, trauma, etc. In exophthalmic goiter we have an exquisitely sensitised organism in which the body functions are dramatically displayed, as if we were projecting on a screen a magnified physiologic picture. Exophthalmic goiter gives us a glimpse of normal physiology with microscopic magnification; iodism alone duplicates the symptoms of exophthalmic goiter.

In those chronic diseases or conditions in which an increased metabolism has continued for a considerable period of time, as, for example, in tuberculosis, in chronic infection, in the rutting season, in pregnancy, in exophthalmic goiter, there is frequently a hyperplasia of the thyroid gland. Each of these states is characterised by increased metabolism, increased heart action, sweating, easily flushed face, mental excitability, disturbed sleep, unstable heart action, unstable sensitised organism, and chronic fatigue. In each, after a period of rest, graded muscular action is beneficial; emotional influences are damaging.

These observations suggest that some cases of chronic exhaustion may be due to the same cause as acute exhaustion; that chronic exhaustion is due to a persistent change in the activating glands. The thyroid and the adrenals may be so altered that their output is increased. If it were found that the thyroid and the adrenal were enlarged, or if the thyroid cells were enlarged, or if the iodin content were altered, the analogy would be sufficiently complete to regard many of the forms of war neurasthenia, disordered action of the heart, 'exertion syndrome,' etc., as belonging to the same class, but not identical with mild exophthalmic goiter. Lieut.-Colonel Schwab has observed symptoms of exophthalmic goiter in many soldiers. It is interesting and significant to note that the same measures that benefit cases of exophthalmic goiter also benefit these other cases—*e.g.* mental rest, simple pastoral existence, most carefully governed muscular activity. Each class is improved by sound sleep, by wholesome, plain food—by a nursery regimen. Each is made worse by emotional excitement, by infection, by injury, etc.

A further point of interest is the fact that patients who have taken too much thyroid extract show many of the same symptoms.

Aschoff and other investigators,[1] by stimulation of the thyroid nerve supply, have shown that the thyroid gland is activated by nerve impulses. A large experience in blocking the nerve supply of the thyroid and in tying the superior thyroid vessels in exophthalmic goiter leads us to the same conclusion. This

[1] Rahe, J. M., Rogers, J., Fawcett, G. G., and Beebe, S. S. P.: *Am. J. Physiol.*, 1914, xxxiv. 72-80; Watts, C. F.: *ibid.*, 1915, xxxviii. 356-362.

view has also been confirmed by Cannon, who joined the phrenic nerve to the sympathetic leading to the thyroid, so that as a result an 'electric charge' came to the thyroid over the phrenic nerve with each respiratory rhythm—thus reproducing the kinetic drive of soldiers when their ' wind is up ' in the midst of shelling and bombing and sniping and bayoneting.

What difference does it make what the driving force is, so long as it is a drive that causes the transformation of energy, and the brain is able to carry its part, the adrenal its part, the thyroid its part, and other organs their part ? In time, one or another vital organ will fail in this stepping-up process, in this increasing pace, until some part of the mechanism fails. When an essential part of the mechanism weakens, there results an impairment of the power of the entire mechanism to do work—there is exhaustion. In exophthalmic goiter, in the infections, in grief, in fear and worry, and in excessive work, no less than in the great drive of war, the mechanism is driven sometimes to acute, sometimes to chronic exhaustion. If the exhaustion is overwhelming and acute, as after injuries, hemorrhage, perforation of viscera, etc., it is called shock. In each case the symptoms are similar ; the causes are identical ; the principles of treatment are the same ; the physical and the chemical phenomena are alike. Perhaps the very great difficulty of finding enough difference among the results of the various causes of exhaustion and shock is sufficient reason why we should aggregate them all into a fundamental inseparable group, the members of which differ only in the extent to which the physical mechanism of each has been altered. What difference exists between the treatment of acute shock from injury and the treatment of acute exhaustion from exertion, from worry, from acute nervous breakdown, from the strain of battle, or from acute infection ? It is always the same—the all-inclusive rest, warmth, fluids, sleep. What more ?

CHAPTER VI

A SUGGESTION AS TO THE MANNER IN WHICH ACTION PATTERNS ARE CREATED IN THE BRAIN

I. The Mechanism of Response to Stimulation

In this chapter we do not presume to present a theory—not even a hypothesis—but rather merely a speculation based upon the electro-chemical theory.

If we assume that the organism is an electro-chemical mechanism, by means of which potential energy is transformed into kinetic energy in the form of heat, muscular action, and electricity, through the co-ordination of certain organs, then the following question naturally follows:—How do stimuli which vary so greatly in their nature and in their intensity reach the brain through the vast numbers of delicate receptors of varying kinds, find their way through the intricate paths of the brain mechanism, and produce each its specific response? That is, how is it that light waves always activate the rods and cones of the retina; the coarser waves of sound the organs of Corti; the infinitely attenuated particles in the air the receptors in the nose? How is it that the activation of these receptor mechanisms, so delicately attuned to such infinitely small waves of motion and of chemical action, can cause responses as powerful as those produced by the gross injury of tissue? A shell wound may cause no more activation than is caused by an intense emotion resulting from a danger that has been seen or heard. The variations in the intensity of the response to an adequate stimulus, the variations in the speed of the response, the relation of the response to variations in the force or in the area of contact of the adequate stimulus will be less difficult to understand if we consider them in the light of the action of certain man-made machines. A motor-car may be started by the laborious process of cranking by hand, or by a light pressure on the starter button; a motor-boat may be guided by a heavy unwieldy rudder, or by intangible wireless waves; the movements of Hammond's artificial dog, with its selenium eye, were governed by rays of light. In the biologic mechanism, if it can be demonstrated that electric energy is released as a result of the application of the adequate stimulus, then these man-made mechanisms make it easy to believe that the brain can be activated to the utmost by infinitesimal stimuli.

We will grant that the man-made mechanisms are infinitely crude, as compared with the human mechanism, which has been evolved through æons by infinite trials, resulting now in error, now in the survival of the evolving animal mechanism. Loeb has shown approximately by what physical and chemical processes the rays of light orientate the simpler animals; how the light rays, acting like photographic processes, move animals adaptively. The approximate photo-chemical mechanism that produces motion toward colours as a means of protection is now known. As stated in a preceding chapter, Piper has demonstrated in fish the presence of electricity in the auditory nerve as a consequence of sound waves. By a simple experiment, Steinach[1] has taken from the field of mystery the means by which the fish maintains equilibrium. Believing that the hair in the auditory sac was the receptor mechanism, he replaced the otolith by a piece of iron of similar shape. When a magnet was brought near this piece of iron, the iron was lifted into a new relation to the hair and in opposition to gravity. This caused the fish to execute bizarre movements, showing that the hair in the sac was in effect a self-starter, which when 'pressed' by the otolith or the substituted iron, closed the circuit, the resultant electric current producing the muscular response. The fish had been adapted to gravity; magnetism suspended the law of gravity and upset the fish. The crude otolith of the fish in its exposed sac is replaced in the higher animals by the semicircular canals filled with fluid. This fluid, like the otolith, obeys the law of gravity; and it may be presumed that, like the otolith, it causes electric contacts to be made and broken, thus releasing and activating electric mechanisms as do the buttons of the self-starters in man-made machines.

We have previously stated that Einthoven and Jolly demonstrated that electric currents appear when a ray of light falls on the retina, and it is common experience that the application of electricity to the eye causes flashes of light. If the light rays falling on the retina cause electricity, and if electricity activates the mechanism by which the sensation of light is produced, then we may infer that light waves falling on this or that group of rods and cones may do for the mechanism of the brain, which responds to light by adaptive actions, what the sound-wave stimulation of the hair in the otolith does to the brain and the muscles of the fish; what the fluid in the semicircular canals does for the adaptive mechanisms of specific response in higher animals; what the hair in the Venus' Fly-Trap causes the plant to do to the fly; what the photo-receptive mechanism of the fish does to its adaptive behaviour; what the selenium eye does to Hammond's artificial dog, or the wireless wave to the distant motor-boat. We infer that the ray of light broken by a shadow caused by the advancing enemy activates the motor mechanism of a soldier

[1] Steinach, *vide* Starling, E. H.: *Principles of Human Physiology*, 1915, p. 603.

to fight or to escape through the agency of a mechanism no less adaptive than are the above-mentioned mechanisms.

The hair of the Sensitive Plant, the hair in the otolith, the fluid in the semicircular canals, the rods and cones in the eye, the photo-receptive mechanism in fish, are self-starters—they are selenium eyes of infinite fineness, but are no less demonstrable and operate no less by physical laws than does the man-made device.

The conception that the brain mechanism is operated by electricity opens the way to illuminating interpretations of adaptive reactions. As Mathews states, all cells are electric batteries. Hence, the large cells in the fundus of the eye, connected with rods and cones, may be regarded as batteries, attuned to be discharged by the electric energy created by the action of the ray of light on the rods and cones. Nernst first proposed, and many physical chemists have accepted the theory, that stimulation is not due to a continuous flow of electricity, but that interposing membranes must first be polarised by the accumulation of ions, stimulation taking place when a sufficient accumulation has occurred. If this theory be true, then a quantitative element is admitted so that we may suppose that the semipermeable membranes, in the case of the feeble electric current set up by a light wave, offer a correspondingly feeble resistance to be overcome before stimulation is achieved. Once the first cell in the path of the electric current is stimulated, and its electric charge is added, then the charges of the other cells lying along the base of the retina will be 'fired' with great rapidity, augmenting the current. In this connection, it is at least interesting to note that the cells which are connected with the rods and cones are both *large* and *numerous*; whereas the nerve endings which act as receptors for physical injury, such as the sensory nerve endings in the skin, have almost no accumulators in the form of nerve-cells to reinforce and augment their stimulus. The inference is that the infinitesimal receptor of the eye, which receives a beam of light of infinitesimal power, has made up for the want of initial physical force by adding a group of accelerating batteries. Were there a set of accumulators in the skin as powerful as those in the eye, endless explosions of energy would result; and besides such a mechanism would be too delicate to estimate correctly the amount of pressure or of injury received by the skin. It is as important that the nerve receptors in the skin should have scant accelerating batteries to *minimise* the strength of the force in their specific stimuli as it is that the eye should have powerful accelerators to *augment* the infinitesimal physical force of its specific stimulus. It is of interest in this connection to note that Nissl found that the cells at the base of the retina became exhausted when the eye was long exposed to sunlight. Precisely similar changes, as we have shown, are found in the brain-cells generally as the result of a crushing traumatic injury. The blindness

produced by sunlight is comparable to the loss of the power to produce body-heat, muscular work or mental action, which results from body-wide trauma. Body-wide prostration is traumatic shock ; sun-blindness is sunlight shock.

A similar line of argument suggests the interpretation of the action of the auditory mechanism. As the passage of electricity through the eye causes the sensation of light, so the passage of electricity through the ear causes the sensation of sound. The organ of Corti bears a suggestive similarity to Helmholz's resonators for the analysis of sound waves ; and the added cell mechanism suggests an electric mechanism specifically adapted to respond to sound waves. Numerous nerve paths lead off from the auditory mechanism. The purpose of these, as of the cells which lie along the base of the retina, may be interpreted by Nernst's law of augmentation or retardation of stimulation.

In like manner, the sensations of touch and pain, of pressure and distention, and the action of the various chemical and thermal receptor mechanisms may be interpreted. In short, no matter how slight the stimulus, or how delicate the mechanism, as long as it will inaugurate a current of electricity, however feeble, then the addition of accumulators can augment to any degree the force of its ultimate electric discharge. The brain cells supply the electromotive force which operates the mechanism. Thus the various types of receptors receive and transmit to the brain an infinite variety of electric currents, from the various receptive mechanisms. These currents enter the brain on equal terms of competition for the possession of what Sherrington calls the ' final common path '—the path of action.

II. The Mechanism of Specific Response—Action Patterns

The preceding discussion suggests the manner in which the electric response to stimulation is achieved, but does not interpret the unfailing specificity of the response ; does not explain how the myriads of electric discharges from the receptor mechanisms emerge as orderly action from the central organ of activation—the brain—with its infinite number of pathways and interlacings and apparent entanglements (Fig. 112). The possibility of these ordered responses seems even more difficult of comprehension when we consider the fact that while the agency by which activation is secured is electric, yet there is no insulation of the pathways in the brain. Further consideration, however, will show that this fact in itself may possibly be the means by which both variety and orderliness of action are secured.

We will assume that the recording matrix does not include the brain-cells but only the non-cellular parts of the brain—the white matter. Are there

any properties of this white matter that would suggest the nature of action patterns ?

1. The white matter is a semi-fluid mass, 85 per cent. being water.

2. The gray matter has a rich blood supply; the white matter has a relatively small blood supply.

3. In the gray matter, cells predominate ; in the white matter, fibres and matrix-like substance predominate.

4. By subjecting both the gray and the white matter to stain for oxidase, Marinesco [1] showed that the gray matter is filled with oxidase, of which the white matter has none. The significance of this finding lies in the fact that the presence of oxidase implies metabolism and oxidation ; it implies the *fabrication* of electric energy, not its *specific conduction*.

5. The gray matter is the working tissue. May not the white be the recording tissue ?

6. The two sides of the special cord and of the brain have a crossed arrangement of the conducting paths ; paths from the left side cross over to the right ; from the right side to the left ; thus apparently complicating the mechanism.

This decussation could not have been evolved in the interests of economy. for it makes the paths longer, hence more material is required ; it could not be to facilitate the rate of action, for the longer distance to be traversed requires more time ; its purpose could not be to secure a more certain blood supply, for no arteries cross ; it could not be to secure co-ordination of the right and left sides, for in that case the responses to unequal stimuli would be the same. That it is an arrangement of the highest importance, we must assume, because it is universal in the higher animals. The brain and the cord are the only decussating organs ; bones do not decussate ; the heart does not decussate ; blood-vessels do not decussate ; the sympathetic nervous system does not decussate. Why does the cerebro-spinal nervous system alone decussate ? Let us examine further the kind of tissue that decussates. White matter consists of highly specialised fats, among which is linolinic acid. Linolinic acid in itself may be supposed to have some interesting qualities in view of a certain property of linseed oil. It has been shown that linseed oil has the power to remember sunlight, and Mathews states that linolinic acid probably has a higher development of the power of memory than linseed oil, which has even a capacity for a limited ‘ education ’ in responding to light. Because of this property, Mathews offers an attractive speculation as to the possibility that memory may be the result of impressions made on the linolinic acid in the white matter.

On the electro-chemical basis, however, we may consider that the commissures, consisting of this white matrix, have been evolved through infinite

[1] In the laboratory of Base Hospital 4 (The Lakeside Unit) in France.

trial and error as a mechanism for recording the *differences* in the magnetic field which accompany every passing specific electric current.

The properties of the receptor mechanism in a wireless circuit are almost as wonderful as those in such a theoretic biologic mechanism. It is conceivable that thus the white matter develops a memory of this or that type of variation in facilitation of the magnetic field resulting from variations in the incoming electric currents from the receptive mechanisms. Through association, therefore, the white matrix will respond in the same manner to a like facilitation from a receptor mechanism, even if days or months have elapsed since the facilitation was initiated.

As for the decussation of the white matrix, may its advantage lie in the possibility that, by sending the active current from one side to the other, the magnetic field is doubled; and in consequence a double impression is made on this matrix of infinitely impressionable material, whose composition never changes during life, and whose constituents are almost unalterable and have no material metabolism?

We may thus conceive that the white matter functions as a multiple phonograph record upon which each incoming stimulus has traced its record. When the brain-cells are again roused to action by a repetition of any one of the stimuli which has traced its original record, the outgoing electric impulses released by the stimulus traverse the facilitated path and reproduce the original action. A phonograph record which has been filed away will give back the same words or tune in after years—why may not varieties of magnetic phenomena be written on the white matter, the recording tissue, and there await recall? But whether these facilitated paths consist of specifically altered pathways, or are the result of varying rates of vibration acting upon some mechanism similar to those which receive the varying rates of vibration which produce light and sound, we have no conjecture to offer.

Such a facilitation as we have suggested would be produced whichever side of the brain received the initial or the repeated stimulus; for if the brain did not decussate, then if one first saw a rose with the right eye alone, the left being closed, it would follow that if the right eye were closed the rose would be a stranger to the left.

We may imagine that decussation pools the path of facilitating action, pools the incoming impulses and the outgoing currents of action, and produces like memories of the impressions received from either side—from either ear, either eye, either hand, etc. If there were but one eye, one ear, one hand, etc., there would be no need of decussation, no need that the right side should know what is done by the left.

As a consequence of these facilitated paths, whatever their physical mechanism, co-ordination of action results instead of chaos. Hence the

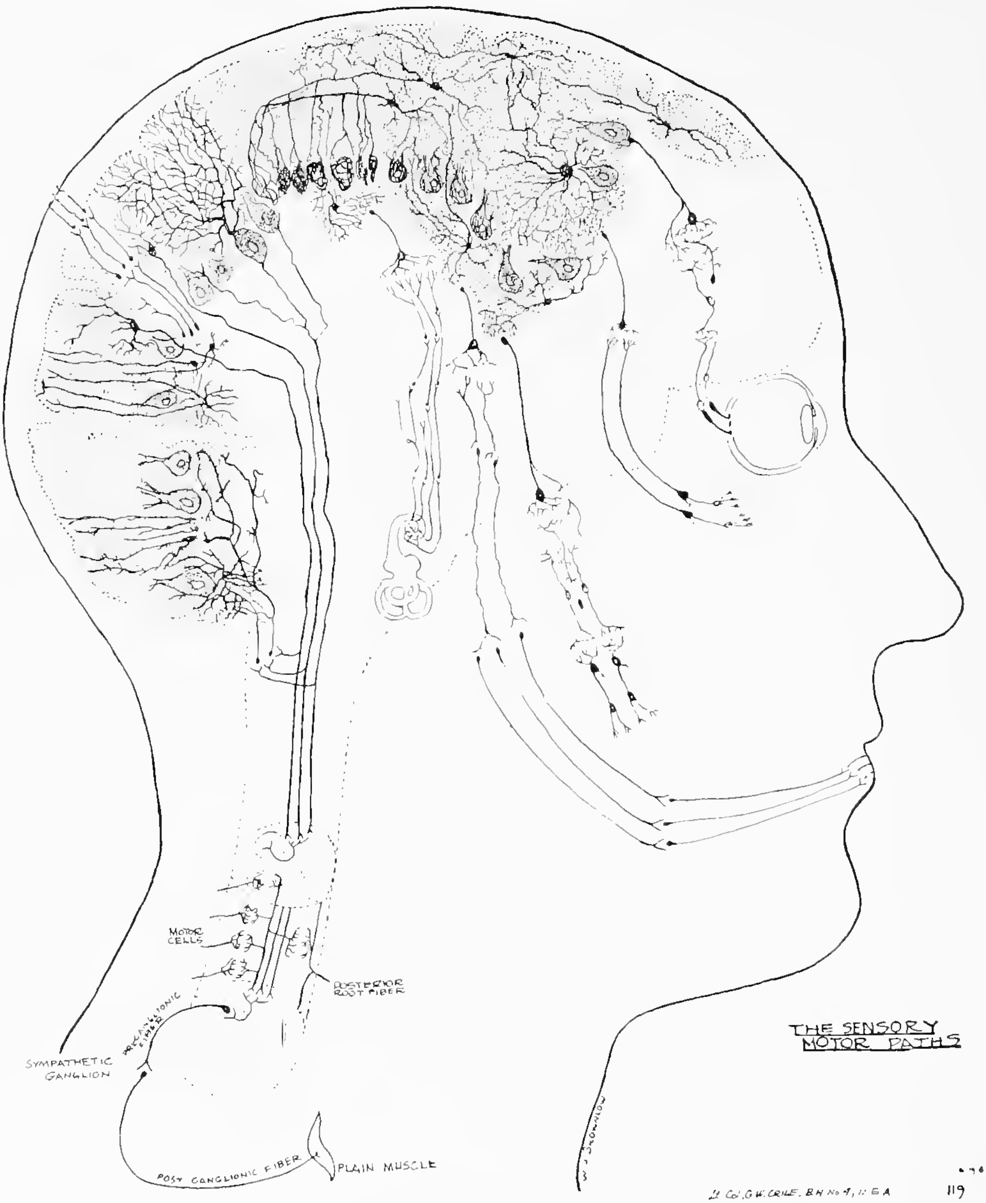


FIG. 112.—Schematic Drawing Illustrating the Various Motor Paths.

stronger the impression made by a stimulus, the better will it compete for possession of the final common path—the path of action. The more frequently an act is performed, the deeper its impression on the white receiving and recording matrix; hence, when an overwhelming abnormally strong action current passes through the brain, it may facilitate a path so abnormally that it dominates all other impulses. Thus a financial or moral disaster, a great danger, a terrible scene may make such an impression—a path of such a degree of facilitation—upon the recording matrix that, from the moment it has been received, no other can compete with it, and the brain, in consequence, becomes approximately a one-path mechanism. Or a like overwhelming facilitation may be produced by the constant repetition of a single act—hence a dominating habit.

Thus, we venture to suppose that the white matter is the matrix on which the action patterns are written; that the cells of the brain supply the electromotive force both for the magnetic field, variations in which produce the facilitated paths of action, and for the resultant activation. It may be that the nerve fibres and the neuro-fibrillæ are made up of concentrations of electrolytes which retain the 'memory' of impulses—thus constituting the facilitated paths (Fig. 112).

Turning from this purely speculative side, let us test the general hypothesis in an interpretation of certain well-known clinical phenomena.

CHAPTER VII

A THEORETICAL ELECTRO-CHEMICAL INTERPRETATION OF CERTAIN CLINICAL PHENOMENA

HAVING summed up certain evidence tending to show that the organism obeys certain physical laws, although our knowledge of those laws and of their operation in the organism is meagre and insecure, it may be worth while to attempt an interpretation of a few familiar clinical conditions.

I. The Mechanism of the Infections—Fever

The effect on the organism of the injection of foreign proteins, as shown by Vaughan,[1] is similar to, if not identical with, the effect of infections. The mechanism of the action of the infections may, therefore, be regarded as the same as the mechanism of foreign protein reactions.

The injection of excessive amounts of foreign protein and the absorption of the toxins of infection produce similar effects, and involve certain essential parts of the same mechanism as the emotions and muscular exertion. This statement is based on the following phenomena :—Each produces an increased output of adrenalin, a first stage of hyperchromatism of the brain-cells, followed later by chromatolysis, increased thyroid activity, increased body temperature. As a result of each, if excess fatigue is produced, the mechanism may be acutely worn down and completely overcome in death. The organism may be partly reduced by any one of these causes, carried further by another, and finally broken by still another. Their effects are interchangeable. Each produces increased electric conductivity of the brain in the acute phase, and in the stage of exhaustion a decreased electric conductivity of the brain. Each produces increased nervousness, and lowering of thresholds to other stimuli.

The first practical question is this :—Is the response of the organism to an infection an imposed injurious mode of attack by the invading micro-organism as a means of killing man and other animals, or is this response one of the evolved

[1] Vaughan, V. C.: *J. Lab. and Clin. Med.*, 1916, i. 631-643; 851-861.

means by which man and animals defend themselves against the attacking micro-organisms? Assuming it to be the latter, let us analyse the mechanism of this counter defence of man against the micro-organism in the light of the principles we have enunciated. If our theory is correct, we must point out the sequence of events from the absorption of the toxin through the period of furious response to recovery or death, and point out the mechanisms which are involved. We must show that the brain is an essential factor in the reaction, and must supply evidence of its work. We must show that the muscles participate actively; that the adrenals are active; that the thyroid participates. We must show why a rise of temperature is of benefit; why there is no sweating in the first stage; why there may be chills. We must show why the temperature falls during the night. We must show why there is nervousness, loss of mental power, loss of muscular power. And last, and certainly not of least importance, we must show why, in an acute, overwhelming infection, there is shock and collapse, with diminished metabolism instead of increased metabolism as in the earlier stages; and why, under such circumstances, death is usually inevitable.

THE PARTICIPATION OF THE BRAIN

(1) It is common knowledge that deep narcotisation with morphin reduces the power of the brain to drive the organism to transform potential energy into heat or into mental or muscular work or to express emotion. We may suppose that for the same reason morphin prevents the electric fish from transforming energy into electricity. In infections, morphin diminishes fever. In the acute phase following the injection of toxins, there is an increase in the conductivity of the brain; in the later stages there is a depression—morphin minimises these changes.

(2) When an animal is first given large doses of morphin, then toxins, the brain-cells show less histologic change and the organism shows less systemic response.

(3) The injection of foreign proteins, or of bacterial toxins, causes first hyperchromatism of the brain-cells and later chromatolysis; but deep narcotisation with morphin diminishes or prevents both the anaphylactic and the foreign protein systemic response and to the same degree prevents the changes in the brain-cells.

(4) Anaphylaxis and foreign proteins and bacterial toxins cause an increased output of adrenalin. Deep narcotisation by morphin prevents both. The significance of this point is that

(5) The brain drives the adrenal glands to their increased output; for when the nerve supply to the adrenal glands is first severed, and no morphin is given,

the injection of foreign proteins, toxins, etc., causes no increased output of adrenalin.

(6) In cases in which there is disintegration of the brain, as in enfeebled aged subjects, but slight fever is produced by even fatal infection. The highest fever and the most vigorous systemic response occur in the earlier period of life when the brain is most active.

(7) After decapitation, or when the muscles are cut off from connection with the brain, there is no febrile response, and the temperature of the body behaves like that of cold-blooded animals. It would seem, therefore, that there are in the brain or nervous system chemical receptors, evolved to drive the brain, which in turn drives the body to make a febrile defence against the foreign proteins brought into the body by bacteria, or by disintegrating body proteins. It appears that the brain responds as adaptively in infections as in running or fighting, etc.

THE PARTICIPATION OF THE MUSCLES

The muscles are obviously the principal mechanisms for making the chemical response to infection, for

(1) They produce from 50 to 75 per cent. of the heat of the body.
(2) They show fatigue and histologic change as a result of high fever.
(3) They are the active agencies in chills.

THE PARTICIPATION OF THE ADRENALS

(1) The output of adrenalin, as shown by Elliott, is increased by foreign proteins, toxins, etc.

(2) Adrenalin alone causes a febrile reaction, *i.e.* the injection of adrenalin causes virtually all the phenomena of infection or of the injection of a foreign protein.

(3) In Addison's Disease, in which there is an adrenal insufficiency, the body temperature is subnormal. In this disease it is stated that infections cause much less rise in temperature, and the body is not so well defended against infection.

(4) In fevers, we may suppose that the dilated pupils, the flushed skin, the dilated nostrils, the opened air passages, the pounding heart, the elevated blood-pressure, as well as the fever itself, result in part from the action of adrenalin.

(5) The injection of adrenalin causes an immediate increased electric

conductance with later decrease, and it produces immediate hyperchromatism of the brain-cells, followed later by chromatolysis.

(6) Adrenalin alone causes leucocytosis; most fevers cause leucocytosis.

THE PARTICIPATION OF THE THYROID

(1) In cases of excessive thyroid feeding, and of exophthalmic goiter, there is an increased metabolism; and infections cause abnormally high temperatures.

(2) In myxedema, the body temperature is subnormal; and, though myxedematous subjects succumb to infections, they show little febrile reaction.

(3) The specific action of the thyroid is due to its specialised iodin. Iodin causes an increase in electric conductance; therefore the effective work of the electric energy created by the brain would be correspondingly increased by the iodin facilitation.

(4) Iodin alone causes most of the systemic symptoms of an infection. It is almost impossible to differentiate between an acute infection and acute iodoform poisoning.

(5) After operations for exophthalmic goiter, who can distinguish with accuracy between the febrile reaction facilitated by the activation of the organism by the hyperactive thyroid and the activation due to an acute infection?

(6) In exophthalmic goiter there is a state of abnormal iodin facilitation, *i.e.*, as we suppose, electric facilitation, and even an acute cold may cause a violent febrile response resulting in death.

(7) In chronic infections, and even in prolonged acute infections such as tuberculosis, the thyroid is frequently hyperplastic.

(8) In exophthalmic goiter, the thyroid is hypersensitive, hence hyperresponsive. Its enlargement is frequently demonstrable during an acute infection. Tonsilitis may cause the thyroid to enlarge and to remain enlarged.

(9) After the removal of infected tonsils, the thyroid sometimes subsides promptly.

(10) In the acute infections, even in the chronic infections, the individual is palpably under the influence of the thyroid. One of the evidences of this is the nervous state of the patient, which is but an indication that the nerve pathways have been facilitated by iodin for the more ready passage of the electric driving force.

The experimental and clinical evidence indicates that a large rôle is played by the thyroid in the defence of the organism against the infections.

THE MECHANISM OF NERVOUSNESS

The evidence of the participation of the thyroid may with equal logic be applied to the mechanism of nervousness.

(1) In exophthalmic goiter cases, the nervousness is similar to that of infections—the restlessness, the tossing and the sleeplessness may be regarded as phenomena of the facilitation of the electric conductance by iodin and adrenalin.

(2) On the next day after a lobectomy has been performed, in an exquisitely nervous, excitable, exophthalmic goiter patient, the one conspicuous change—conspicuous to the nurse, and of infinite comfort to the patient—is the diminution of the intolerable restlessness, intolerable excitability. We may suggest, therefore, that the nervousness in fever is due to the increased action of the thyroid. Do myxedema patients show an equal increase of nervousness in infections ?

THE MECHANISM OF TEMPERATURE PHENOMENA

Fever.—We have suggested the mechanism by means of which increased chemical activity, including fever, is produced, but the following question remains : What adaptive purpose is served by the increased temperature ? This question is of peculiar significance in view of the obvious fact that this mode of defence is itself injurious to the organism, sometimes causing permanent injury or death.

(1) First of all, we may assume that the chemical invasion of bacteria can be met only by a chemical defence.

(2) We may suppose that the foreign protein molecule in an environment foreign to it will be split up more readily than the living protein molecule of the defending organism ; therefore, the more intense the chemical action of the defence, the more certainly and readily will the foreign protein, living or dead, be split up ; that is to say, the defence of the body against foreign proteins, such as toxins, is a ' purification by fire.'

(3) With each degree of rise in temperature in a physical or a biologic system, chemical activity—hence metabolism—is increased 10 per cent.

(4) With each degree of rise in temperature, the electric conductance—hence the driving power of the brain—is increased 2·5 per cent.

(5) The organism must maintain a standard of chemical purity, and this

standard, as we suppose, is reached by burning the foreign proteins in the furnace of the living through intense chemical action, intense oxidation. The foregoing does not apply to the defence of the phagocytes, nor to defence by antibodies, but only to the defence against foreign proteins.

Dry Skin.—If the full benefit of the increased body temperature is to be secured, heat must be retained in the body. Sweating produces cooling of the body as the result of evaporation. Hence, in infections we have the high temperature with a dry skin in contrast to the active sweating which results from muscular exertion, when heat is not desired.

Chills.—It is obvious that the active muscular contractions of the entire body in the chills which frequently accompany inauguration of the response to an infection are but an added means of increasing chemical metabolism, just as shivering is a part of the process of increasing metabolism on a cold day. On the other hand, it is equally obvious that a man in surgical shock cannot shiver, because the electro-chemical mechanism that fabricates the chill has broken down.

Why does the Temperature fall during the night?—The foregoing suggests that it is because the brain, being the driving battery, must be recharged. This recharging process is probably the state of sleep, but in order that the chemical defence may be as little interrupted as possible the recharging process of sleep is light and short. During sleep the temperature falls because the brain is driving the mechanism less forcibly. All of the brain does not sleep, however, nor do all the glands or involuntary muscles sleep, hence the temperature remains above normal, although it usually falls below the day-level.

The conception that the brain is the battery that drives the chemical mechanism to produce heat explains also the fact that the temperature is lowered by morphin. Morphin diminishes the driving power of the brain. Therefore the mechanism by which morphin lowers the temperature is the same as that by which it diminishes muscular exertion, emotion, and pain, and minimises surgical, anaphylactic, and foreign protein shock. Sleep, morphin, and rest produce similar end-effects.

THIRST

When the biologic electro-chemical mechanism is excessively driven in a strong defence against foreign living and dead proteins, much water is used. Fresh water is a good solvent; it assists in carrying off waste material; it dilutes acids; it wets the tissues—hence *thirst*. Therefore, plenty of water in fevers is demanded and seems to serve a specific purpose.

THE MECHANISM OF COLLAPSE AND DEATH IN OVERWHELMING INFECTIONS

We have seen that just as gazing directly at the sun breaks down the photo-electro-chemical mechanism of sight, in like manner when the sensitive areas and nerves of the body are heavily traumatised, the internal lesions of the brain-cells are so great that they cannot continue their normal internal respiration and become unable to transform potential energy into electric energy at a normal rate ; hence, the power to perform muscular work, mental work, and glandular work is lessened ; the power to maintain the blood-pressure is diminished ; the power to produce the normal amount of body heat is lost. The resultant state is called *shock*. Since foreign proteins drive the brain-cells just as they are driven by emotion or by physical injury, it follows that when there is an excessive foreign protein stimulation, such as results from perforation of the intestines, from the penetration of an abscess into a large absorbing cavity, from anaphylaxis—the brain-cells are overwhelmed by the stimulus, suffer an internal disarrangement, become unable to perform normal work, and may be driven to their ultimate destruction—to death.

It is not surprising, then, that precisely the same principles of treatment hold for the shock of acute infection as for traumatic shock ; that the same agents that aggravate shock, aggravate fevers—*i.e.* injury, fear, worry, loss of sleep, ether and chloroform anesthesia, muscular exertion, etc.; and on the other hand, that precisely the same principles of treatment hold for both the acute and the chronic forms of infection—rest, fluids, morphin, sleep. It would be expected that both acute and chronic infection would produce identical lesions — neurasthenia, myocarditis, nephritis, sweating, insomnia, and that the addition or the withdrawal of physical injury or of emotion or of exertion may quantitatively modify either.

Infection, like each of the other causes of exhaustion we have considered, may be regarded as an activation of the same electro-chemical mechanism ; each is an excitant of energy-transformation ; in each case the energy is transformed by the same organs ; in each case, when the kinetic drive has been so intense or so prolonged as to produce a permanent change in the driving battery or in any of the activators, *exhaustion* follows. Anaphylaxis, with its momentous chemical blow, may be likened to a bolt of lightning striking an electric battery.

The wastage of war and the wastage of over-driven civilian life alike may follow the application of one cause of exhaustion alone, or of any combination of causes. The resultant permanent changes may be a lowering of the brain

thresholds ; the enlargement of the thyroid ; suboxidation due to a heart lesion ; lesions of the liver, etc. Whatever reduces the factors of safety which guard the internal respiration—the central factor in energy-transformation—may cause this or that type of chronic impairment, which means a permanent diminution of the electro-motive force of the organism.

II. The Mechanism of Exophthalmic Goiter

Iodin increases the electric conductance of living tissue ; iodin increases permeability ; increase in permeability increases function. It is apparent that the thyroid gives off its iodised protein adaptively in exertion, in emotion, in infection, in procreation, etc.

Aschoff and others have shown that stimulation of the nerve supply of the thyroid causes a discharge of iodin ; hence, we may suppose that the output of iodin is in part at least under the control of the nervous system. In exophthalmic goiter there is marked nervous activity, and we may suppose that the thyroid is under active stimulation ; that this is the case is shown by the low iodin content of the gland in exophthalmic goiter. Cannon states that adrenalin activates the thyroid. We assume that the activated thyroid throws out large amounts of activating iodin, which by so much facilitates permeability, hence increases activity of the body, including the activity of the thyroid itself and of the adrenals. Oxidation is the basic process in metabolism ; adrenalin increases oxidation ; iodin increases electric conductance, hence increases metabolism (see Fig. 87).

Therefore, through the mediation of the nervous system, a reciprocal interaction is established among the thyroid, the adrenals, and the nervous system. Iodin alone, adrenalin alone, thyroid extract alone, emotion, exertion, or infection alone, each causes a 'Kinetic Drive' with phenomena similar to those of exophthalmic goiter.

If the foregoing interpretation be correct, then the drive of exophthalmic goiter should be diminished by lessening the activity of any one of the three interacting organs—of the brain, by rest cure ; of the thyroid, by its resection ; of the adrenals, by the removal of a portion of their tissue, though evidence of the positive value of the last-named procedure is thus far incomplete.

Nothing in surgery is more striking than the immediate benefit of surgical treatment of exophthalmic goiter. Among 2477 partial thyroidectomies performed by me, 1306 were for exophthalmic goiter. In the expression of the disease, in the behaviour before, during, and after operation, the exophthalmic goiter patient presents notable evidence in support of the mechanistic theory.

It is of interest to note that the active principle of thyroid secretion has

been synthetically produced by Kendall;[1] adrenalin is synthetically made and electricity is made; hence, the equivalents of the activators of exophthalmic goiter, of emotion, of exertion, and of fever may be made in the laboratory.

Among the by-products often noted after thyroidectomy are :—

(*a*) A decrease in the systolic pressure and less frequently a decrease in the diastolic pressure.
(*b*) Diminished nervousness.
(*c*) Diminished myocarditis.
(*d*) General restoration of the widespread impairment due to the excessive speeding of the kinetic system.

In a case thus relieved, an overdose of thyroid extract will re-establish the symptoms. The post-operative state of serenity of the exophthalmic goiter patient is comparable to the colourless state after one has passed through a great emotion.

III. The Mechanism of Malignant and Benign Tumors and of their Treatment by Radiation

Physical chemists (McClendon, Lillie, Loeb, etc.) have shown that fertilisation of the ovum is attended by an increase in permeability; that the state of activity of cells, whether in fabricating or in multiplying, is attended by an increase in permeability. From this, the inference would be drawn that the electric conductivity of cancerous tissue would be increased above the normal. Clowes, in a personal communication, states that he has found the conductivity of cancer tissue to be above normal, and his findings have been confirmed by our measurements of the electric conductivity of tumors.

The thyroid offered a good field for comparative measurements, and sixty thyroids with and without tumors have been measured. Cancers and adenomata showed a high conductivity; the hyperplasias came next, and the conductivity of the colloid goiters was the lowest of the pathological tissues studied.

In this connection it is of interest to note that 2 per cent. of our series are malignant: and that all malignancies occur in adenomata. Adenomata show a high conductivity. Cancer shows a high conductivity. We noted that a papilloma of the ovary of moderate malignancy showed a distinctly lower conductivity than a scirrhus of the breast. The outer growing part of a cancer showed a high conductivity in contrast with a low conductivity of the central non-growing part—a contrast between activity and exhaustion in growth.

[1] Kendall, E. C.: *J. Biol. Chem.*, 1919, xxxix. 125-147; 1919, xl. 265-334.

We should at least ascertain whether or not, in conductivity measurements, we have an added criterion whereby to estimate the presence of malignancy. If irritation of tissue is followed by repair, and if repair is achieved through increased cellular conductivity, a side light on the relation between irritation and conductivity, and the progressive steps leading to new growth, may be found.

It may be worth while to recall that radiation—X-ray, radium, fulguration—to some extent acts selectively on some tumors and cancers. The question may at least be raised whether or not, because of the markedly increased conductance of tumor and cancer tissue, a greater quantity of the radiant energy passes through them, while less passes through the neighbouring normal tissue, as the lightning selects a path through the highly conductive lightning-rod. This increased conductivity may prove to be a sign of malignancy. Indeed, it would follow that cancer tissue, by its high conductance, should measurably shield the adjacent normal tissue with lower conductance. On the other hand, actively functioning tissues, such as the parenchyma of the ovary and the testicle, the cells of hair follicles, etc., should attract more current, hence would be destroyed more readily.

IV. The Mechanism of Inhalation Anesthesia

ETHER

When an animal or a man is given unlimited ether anesthesia, several striking phenomena are observed. First, there is a period of excitement; second, a period of quiet anesthesia; third, a period of profound anesthesia, ending in death.

Period of Excitement.—During the period of excitement, the subject tends to struggle, the face is flushed, there are sweating, moderate or violent muscular action, rapid respiration, dilated pupils, elevated blood-pressure, accelerated pulse, increased output of adrenalin, hyperchromatism of the brain-cells; the consumption of oxygen may be increased up to 150 per cent.; of carbon dioxid up to 325 per cent. (Alexander and Cserna);[1] the H-ion concentration of the blood is increased; the electric conductivity of the brain is increased. If, in the midst of the stage of excitement, the inhaler be removed, the expression of the face resembles that of acute muscular exertion, of acute fever, of acute emotion, of the injection of adrenalin, or of an active phase of exophthalmic goiter. In short, in the early stage of ether anesthesia, there is a mimicry of any one of the great kinetic drives.

[1] Alexander, F. C.: *Biochem. Ztschr.*, 1912, xliv. 127-139.

Osterhout, Overton, Meyer, Lillie,[1] and other observers have shown that ether anesthesia in lighter doses increases the permeability of the semi-permeable membranes of cells to the passage of ions. The activity of cells is governed by the state of permeability of their membranes to ions (Lillie). This increased permeability renders the brain extremely excitable in light ether anesthesia, and therefore it drives the organism to perform more work, as has been shown by Alexander and Cserna, by our researches showing the production of hyperchromatism, by Elliott's demonstration of diminished adrenal content, and by our demonstration of increased adrenalin output. The clinician sees even more striking evidence of this increased activation of the brain in the behaviour of his patient under light ether. In exophthalmic goiter cases, the organism is especially sensitised, and in these the first stage of ether anesthesia gives striking evidence of increased activation. As stated above, we may conceive that this striking activation of the organism and the consequent increase in metabolism in the early stage of ether anesthesia is due to an increased permeability of the membranes of the brain-cells.

We may suppose that ether causes a great increase in the metabolism of the cells, a great increase in the formation of electric energy, which escapes readily through the lowered resistance of the cell boundaries and of the synapses, and in consequence we may presume that heavy charges of electricity are freed from the cells, and run over the open nerve paths leading to the various muscles and glands. There being no adaptive lead over any facilitated action pattern, the muscular and the glandular response is as free from purposeful action as in a convulsion—and, indeed, in many respects, the first stage of anesthesia resembles a general convulsion. Both a convulsion and the first stage of anesthesia are overcome by more ether; but if the victim during this time is held or injured, then the electric action current is led over the corresponding facilitated paths and is concentrated on the muscles required for action, and other muscles become idle. If no contact gives the direction, however, then the outflow of energy is as general as in epilepsy. Just as in epilepsy, there are contractions of all the muscles; there is increased secretion of the salivary and the mucous glands; there is increased sweat; and probably the adrenalin output is increased.

As we have stated, if restraint or injury is applied, then the muscles that usually respond receive all the collective electric force of the brain, and show almost supernatural power. If the anesthetic is withdrawn at this stage, the permeability of the cell returns to the normal, the struggle ceases, the flushed face fades, the sweat and the saliva and the mucus rapidly become

[1] Osterhout, W. J. V.: *Botanical Gazette*, 1913, lv. 446-451. Overton, E.: *Studien über die Narkose*, Jena, 1901. Meyer, Von H. H.: *loc. cit.* Lillie, R. S.: *Am. J. Physiol.*, 1911-1912, xxix. 372-397.

normal, the muscles come under voluntary control and are quiet. The individual appears normal with the exception of a slight fatigue.

Stage of Even Anesthesia.—If the administration of the anesthetic is steadily continued through the stage of excitement, or if the amount is increased, the struggle soon passes into a stage of complete relaxation. The face remains red, although not as red; the eyes suffused, but not as suffused; the skin moist, but not as moist; the saliva and mucus remain abundant, though not as abundant. The H-ion concentration of the blood increases with the increase of anesthesia. In this stage physical injury and restraint cause no marked muscular response.

This is in accord with the findings in our electric conductivity investigations, which showed decreased conductivity of the cerebrum in deep ether anesthesia, as contrasted with the increased conductivity in the stage of excitement. Moreover, Lillie, McClendon,[1] and other biochemists tell us that in this stage of ether anesthesia there is an opposite effect to that of light ether on the permeability of semipermeable membranes to ions, viz. in this stage there is an interference with the increase in permeability of the cell membrane and of the synapses to the passage of ions, hence stimuli are unable to activate the effector mechanism, and in consequence the irritability of the organism is in part lost. In this stage of anesthesia the organism cannot do adaptive work; it is unconscious.

Since it requires far more anesthetic to anesthetise the cell than the synapse—perhaps six times as much—it seems probable that anesthesia is due to a block in the synaptic membrane like that which is supposed to occur in sleep, the difference being that in sleep the synaptic block is at once overcome by stimuli, hence is adaptive; whereas in anesthesia, the block is physical and non-adaptive. For this reason stimuli do not wholly awaken the patient, but nevertheless the afferent impulses reach the brain-cells and stimulate them without purpose—exhausting them without causing awakening—exhausting the brain just as if no anesthetic had been given.

Profound Anesthesia: Death.—If the anesthesia is pushed still further, then there is reached a point of saturation at which the H-ion concentration of the blood passes the neutral point. This is the fatal point, for when the anesthetic causes actual acidity of the blood, death takes place immediately. Death, we assume, is due to the loss of difference in potential in the autonomic and sympathetic, as well as in the cerebro-spinal system; hence, electric impulses cannot pass, and life ends.

The several parts of the brain differ greatly in their response to ether. It would be expected that the brain as a whole would be more markedly affected

[1] Lillie, R. S.: *loc. cit.* McClendon, J. F.: *Science*, 1914, xi. 214; *Am. J. Physiol.*, 1915, xxxviii. 173-179.

than other tissue, such, for example, as muscle, because the brain contains a greater proportion of lipoids, which are especially affected by ether. We would expect also that the order in which the different portions of the brain are affected would depend upon their relative irritability—the more irritable portions being affected first. This we find is true, for first consciousness is lost, then muscular activity, while the centres governing respiration and circulation are but slightly altered. Were the muscle-cells more sensitive to anesthetics than the brain-cells, then the function of the voluntary and of the involuntary muscular systems would fail before the function of the brain, and man would be paralysed while conscious, as in curare poisoning; and since the respiratory and the circulatory muscles would fail, unconsciousness and death would follow the muscular paralysis, and no such state as anesthesia could be established. It is because of this difference between the muscle-cells and the brain-cells that anesthesia and not death is first produced by inhalation anesthesia.

When ether anesthesia is continued for four or more hours, these outstanding facts are noted :—

(1) Gradually less anesthetic is required.

(2) An increasing period for recovery is required.

(3) The brain-cells, the liver-cells, and the adrenal-cells show the same cytologic changes as are seen in exhaustion from other causes.

(4) The reserve alkalinity is decreased.

(5) The H-ion concentration of the blood is increased.

(6) The electric conductivity of the brain is decreased; the electric conductivity of the liver is increased.

(7) The individual is in a state of exhaustion, requiring a period of time for recovery about equal to that required for recovery from an equal degree of exhaustion from other causes.

NITROUS OXID-OXYGEN

In nitrous oxid-oxygen anesthesia, there is apparently an interference with the use of oxygen by the brain-cells. Therefore the brain-cells are able to respond to trauma and other stimuli only in inverse proportion to the depth of the anesthesia. The brain-cells, therefore, are protected against shock. This is demonstrated by the hyperchromatic or normal appearance of the brain-cells after prolonged nitrous oxid anesthesia; and by their normal appearance after shock-producing trauma under nitrous oxid-oxygen anesthesia as compared with their disintegration after like trauma under ether anesthesia. It is demonstrated also by the fact that the electric conductivity of the brain is decreased by long ether anesthesia, while it is increased or unchanged by

nitrous oxid-oxygen anesthesia. These findings are in accord with the kinetic theory and with the conception that the brain is the primary seat of injury from excessive stimuli. The effect of nitrous oxid is somewhat comparable to that of sleep, as our experiments have shown.

Because of the action of nitrous oxid on the intracellular oxidation, its use is fraught with danger unless it is skilfully administered. An animal may be much more quickly killed with nitrous oxid than with ether.

V. The Mechanism of Tetanus and of Strychnin Poisoning and the Synaptic System

(1) The nervous system consists of *neurons*.

(2) Neurons are nowhere in direct physical contact with each other, hence the brain is disconnected from muscle, gland, etc., except during stimulation. During stimulation, the circuit is closed as by a *key*.

(3) The connecting *key* between *neurons* is the *synapse*.

(4) The *synapse*, as suggested by Sherrington, may be endowed with special properties: 'It might restrain diffusion, bank up osmotic pressure, restrict the movement of ions, accumulate electric charges, support a double electric layer, alter in shape and surface tension with changes in difference in potential, alter in difference of potential with changes in surface tension or in shape, or intervene as a membrane between dilute solutions of electrolytes of different concentration or colloidal suspensions with different sign of charge.' [1]

(5) The *synapse* may be regarded as an highly adapted switch which now closes the circuit, now opens it; now diminishes the current, now accelerates it. This living *switch* or key may be the site of the activation of tetanus or of strychnin convulsions. It may possibly determine sleep or the action of certain anesthetics.

(6) An electric current flows from an area of a higher to an area of lower potential, hence the electric battery—the nerve-cell—would be in constant action, excepting for the intervention of the synaptic switch. If the nerve-cell and the end-organ were constantly connected, then the nerve-cell would be in the position of the battery of a door-bell whose button is pegged. With the living electric circuit closed at the synapse, the nerve-cell would work continually and would be exhausted just as certainly as the electric battery in a closed circuit becomes exhausted. And to the same extent the stimulated organ—the gland-cell, or the muscle-cell—would be worn by continuous stimulation. The presence of a synapse as a mechanism of adaptive electric connection and disconnection is as important as the spring which breaks the

[1] Sherrington, C. S.: *The Integrative Action of the Central Nervous System*, 1906, p. 17.

electric current of the door-bell when the pressure is released. Conversely, the presence of the synapse supports the conception that there is an electric potential in the living neurons; that the nerve-cells act in some such manner as do accumulators.

STRYCHNIN

We may suppose that strychnin acts on the synapses in such a way that the electric circuits of many cells are closed at once, so that there results a universal and violent stimulation of muscles constituting a convulsion. Not only is there stimulation of the muscles, but other mechanisms are stimulated also.

(1) There is an increased output of adrenalin.

(2) The blood-pressure rises very high.

(3) There appears a complete cycle of changes in the brain-cells; first a stage of hyperchromatism, then a stage of chromatolysis, and finally, in some cells, swelling, rupture of the nuclear and the cell membranes, and final death of the cells.

Now all this has occurred without the aid of external stimuli; strychnin stimulation occurs under ether anesthesia; the high blood-pressure and the rapid heart and the brain-cell changes occur when the animal is under curare. When an animal is under the influence of a physiologic dose of strychnin, a slight stimulus is enough to overcome the low threshold and produce a convulsive discharge of energy. On pages 26-33 we have presented evidence that strychnin alone can cause exhaustion of the vaso-motor mechanism.

TETANUS

We may assume that the stimulus from tetanus toxin, like that from strychnin, passes along the axis cylinders of the nerve fibres until it reaches the synapses. As with strychnin, when the stimulus reaches the synapses, we may presume that their adaptive response is an extreme lowering of their resistance so that a strong current of electricity is released, causing a convulsion. Is it conceivable that closing the circuit at the synapse 'pegged the door-bell,' and a vast muscular area became in effect one pole of a great battery, the other pole being the brain, the nerves being the connecting wires whose circuit was closed by the action of the tetanus toxin?

The conception that in the response to strychnin and to tetanus toxin the muscular areas alone are concerned, is consistent with the remarkable fact that in tetanus and in strychnin poisoning the intellect remains clear and tranquil until near death. On the other hand, in the adaptive response to the driving of such stimuli as emotion, exertion, physical injury, etc., the response

is not only muscular, but also the intellect is profoundly disturbed. Tetanus causes a relatively slight increase in temperature, and in general there is little evidence of any direct excitation of the brain. In emotion and infection there is a rise in temperature.

VI. The Bio-Electrical Reorganisation of Disabled Organs and Tissues

(1) Electricity, or its equivalent—physiologic activity—is apparently the means by which cells are organised, for, as Sherrington points out, if the eyelids of puppies be kept closed, the related brain-cells will not be developed.

(2) If the nerve supply to muscles is cut off, the muscle-cells become disorganised; but electricity will reorganise them.

(3) Children who are not allowed to play do not develop strongly; that is to say, their muscles are not organised by the electric energy of exercise.

(4) If groups of muscles are not used, they are not so well organised and become weak.

(5) It is probably through the power of the electric organisation of play and exercise that children may be systematically built up into all-round physical efficiency.

(6) When limbs are fractured or soft parts injured, voluntary exercise best reorganises the muscle and nerve cells from the disorganisation of disuse.

Next in value to the voluntary use, which exercises the driving nerve-cell as well as the driven muscle, is electric stimulation of muscle. Electric stimulation restores the muscle quite as well as voluntary stimulation, but electric stimulation does not as readily reorganise and build up the deteriorated nerve-cells.

These points are being abundantly proved by experience in the treatment of the multitude of cripples produced by the war.

(7) In accordance with the conception that the brain is a plastic matrix, in which facilitated conduction paths are made by the passage of action currents, and that the repetition of these action currents increases the facilitation, and that, as the facilitation increases, other action patterns, with greater difficulty, hence less frequently, obtain possession of the final common path (Sherrington)—the path of action—we may conclude that whenever this receptive human matrix of infinite delicacy is exposed to action currents of unusual intensity, as from the fracture of a leg, the pathway of that action pattern in the brain will become dominant; and that, as the recurring pain of dressings increases the facilitation of this pathway, the individual will become largely a one-path individual—*i.e.* he possesses a broken-leg-path brain.

As a result, during this period of painful convalescence, he is less interested in his personal affairs, in his business, in his church, in his philanthropy, in his family, in his friends—his brain is under a broken-leg facilitation.

Abnormal facilitations—one-path personalities—are caused not only by traumatic stimuli, but to the same degree by mental and emotional stimuli. A proud and ambitious financier loses his fortune in a speculation. The action currents of the episode write that record deeply in the facilitated paths of his plastic brain. His brain becomes a one-way brain—a financial-disaster brain! Moral disasters also create one-path brains. In the soldier exposed to the intensive drive of battle, a bursting shell with its noisy demonstration dominates his brain by facilitating the auditory paths of action. The deafening and terrifying explosion has the power of facilitating the action pattern so overwhelmingly that a pathway of unparalleled facilitation is made; and his brain becomes a one-pattern brain—a sound-facilitated, or a shell-shock brain.

Now, if the facilitated action pattern of the 'broken-leg brain' is suddenly subjected to the competition of a strong mental or moral stimulus, such as financial or moral disaster on the one hand, or a long-hoped-for, long-striven-for success of the utmost value on the other hand, then the broken-leg pattern may meet a stronger competitor, and another set of stimuli will gain possession of the 'final common path.' Or, if the bed of the patient catches on fire and his body is extensively burned, the broken-leg facilitation is overcome by the more intense burn facilitation. If the ruined financier suddenly redoubles his original fortune, the good-news facilitation will dominate the failure facilitation.

If the shell-shock brain receives a competing stimulus, such as suffocating anesthesia, a bullet or shell wound, or news of a way to escape from the hazard of war, the shell-shock facilitation may be superseded by one or more other facilitations. By the dominating influence of a psychiatrist, competing action patterns are at once created and the shell phenomena are no longer in supreme control. But the shorter the time since the financier has lost his fortune, the more readily will the facilitated action pattern fade away and be replaced. The earlier the disused muscle in an injured leg is exercised, the better the recovery. The more promptly the shell-shock facilitated brain has competing paths established, the sooner and the more completely will the *normal* stimuli be able to compete successfully, and in consequence a balanced personality be restored.

Our action, our behaviour during every day, every hour, in every phase of life, may be regarded as the expression of the succession of action patterns that gain possession of the common path. The psychiatrist, with infinite skill, visualises and analyses the human phonograph record; he hears it play

the tune of life by sampling it here and there ; he sees what records are too much facilitated, what records are depressed for want of use as a result of the domination of competing paths, and he then facilitates this path and depresses that by his trained and acquired skill and power of playing at will the electro-chemical mechanism ; and thus before his eyes he sees a transformation of the organism. In the great war, the psychiatrist, by suggestion, has done for the brain mechanism what the surgeon has done by nerve suture for the nerve-muscle mechanism ; what the internist in the training camp does for the exertion syndrome, and what training and discipline does everywhere. In war, after the principal defects in the local mechanisms are corrected in the training camp or in the hospital, the man, with his partially restored electro-chemical mechanism, is turned over to the combatant officer, who co-ordinates the whole into a standardised human unit of combat.

CHAPTER VIII

PRACTICAL APPLICATIONS OF THE KINETIC THEORY IN TREATMENT

I. Water, Opium, Oxygen, Heat, Sleep

Water.—Water and oxygen and sleep are too abundant, too secure, too commonplace to attract our attention. We are prone to assume that we know all about water because we know its formula is H_2O. In infections, in surgical shock (acute exhaustion), we are apt to think of water chiefly as a possible therapeutic agent for raising and sustaining the blood-pressure. If water does not raise and sustain the blood-pressure, then we are too ready to conclude that water has no virtue in the treatment. We forget that its function has little to do with blood-pressure. We forget that water is the vehicle in which the electro-chemical mechanism is suspended and has its being: that water is the basis of life itself; that man will live longer without food than without water; that the properties of water of biologic importance are not all known to physicists and biologists. Among the properties of water known to be vitally useful to the organism are the following:—

(*a*) Water has a greater specific heat than any other substance.
(*b*) Water has the greatest solvent power.
(*c*) Water has the greatest power as a catalyst.
(*d*) Water is the only medium in which colloidal systems can be established.
(*e*) Water itself is a great chemical activator.

We forget that it is not improbable that man is a multiple descendant of his ancestral water-born unicellular marine organism; that man has emerged through evolution from the sea, bearing the formula of the sea, and that some parts of his body are almost as liquid as the sea; that he is a landed marine animal, obeying the laws of the sea. When a patient has reached a stage of physico-chemical dissolution in which his tissues no longer absorb and use water, it does not mean that *water* has failed; it is a sign rather that the organism has failed, and that irrevocable dissolution is in progress. The patient should have water early as well as late, and should have enough water,

in the interest of his internal respiration and basic metabolism rather than of his blood-pressure.

Opium.—Opium is the most useful and the most harmful of all drugs. Our theme in this volume has been to adduce evidence of medical interest tending to show that man is an electro-chemical mechanism evolved to transform energy adaptively; that in the transformation of energy, whatever its purpose, a group of organs collaborate. Whether the purpose of the transformation of energy be for the pursuit of prey, the cultivation of a field, escape from an enemy; whether for the mobilisation of a chemical defence against an invading micro-organism; whether for procreation or in response to physical injury; whether for emotion—whatever its cause or purpose, energy-transformation in the organism is diminished or controlled by opium. This control is evidenced by the facts that under deep narcotisation with opium, the adrenalin output is blocked, the permeability of the brain and of the liver is relatively stabilised, and brain-cell and liver-cell changes due to infection or injury are diminished. Under opium, neither emotion nor muscular exertion can be expressed; the temperature and pulse and respiration of infection are measurably controlled, anaphylaxis is averted, and surgical shock greatly diminished. Opium reduces the total metabolism under all circumstances in which the brain is the driving cause of the metabolism; but opium apparently has no power to prevent the increased metabolism produced by the injection of adrenalin. Opium, therefore, controls the *output*, not the *action* of adrenalin. Opium has not the power to prevent strychnin convulsions, despite the fact that it prevents voluntary muscular contractions.

From these considerations we conclude that opium controls the electro-chemical mechanism of man by blocking its battery—the brain and nerve cells. Hence, opium solaces the troubled, controls pain, diminishes the drive of fevers. Opium—deep opium narcosis—is, therefore, a boon in traumatic shock, in septic shock, in anaphylactic shock, in shock due to pain. On the other hand, opium is of no value, but does harm, in tetanus, in asphyxia, in acute acidosis. Opium, through its power of blocking vital processes, which are governed by the nervous system, interferes much with important glandular activity. Therefore, when a patient is under deep narcotisation by opium, *there should be given a subcutaneous infusion of from* 2000 *to* 3000 *cc. normal saline solution*, and 5 per cent. solution of sodium bicarbonate and glucose should be administered per rectum, to the end that the desiccating effect of opium may be overcome and the tissues be duly wetted, and that the elimination of waste products may be facilitated. There is evidence that, in addition, under certain conditions, oxygen under pressure should be added.

Oxygen.—There is but little to say about oxygen, for the respiratory mechanism, unlike the circulatory mechanism, deals with the light mechanical

forces of air, not with the heavier forces required for circulating the viscid blood through a vast system of resisting vessels. One point should be borne in mind, however :—The respiratory centres may become so altered that they no longer respond normally, and there results anoxemia—deficient aeration of the blood ; an extremely dangerous condition. Anoxemia is characterised by three outstanding clinical features :—

(*a*) The respirations are either too shallow or too slow, and are obviously exercised by a tired centre.
(*b*) The patient is ashen gray or gray-blue.
(*c*) The patient is in profound prostration.

The one obvious therapeutic measure is the administration of oxygen under pressure to improve the internal respiration of the tissues.

In the war, this condition was seen among three classes of patients : cases of phosgene poisoning ; patients in late traumatic shock ; some patients with chest wounds. Each showed like phenomena ; each required like treatment, viz. oxygen under pressure. But a conscious patient is apt to rebel, even to struggle against inhalation under pressure. This may be obviated by using the nitrous oxid-oxygen apparatus, giving sufficient nitrous oxid to take the edge off the anxiety—merely analgesia. In this pleasant state, oxygen under pressure may be given without the disadvantage of exciting the opposition of the patient.

Heat.—Heat may play a prominent rôle, both in the production of shock and exhaustion, and in restoration. The organism of warm-blooded animals performs its functions best at an optimum, even temperature. If the temperature is raised much *above* normal, there is exhaustion ; if depressed much *below* the normal level, there is exhaustion. The laws of physics establish the effect of temperature on chemical processes. With each degree of rise in temperature, chemical activity is increased 10 per cent. We have suggested that, in making a defence against infection, heat is a valuable aid in accelerating the defending chemical action of the host. Is it possible that the good effect of the application of local heat to infected areas may in part be due to an increase in the defending chemical activity of the phagocyte ? In excessive fever, which threatens life, the reduction in temperature by cold may owe its benefits, in part, to the consequent diminution of the excessive chemical activity. Not only does increased temperature accelerate chemical activity, but it increases electric conductance—*i.e.* each degree of rise in temperature increases electric conductance 2·5 per cent. Increased electric conductance automatically causes an increase in metabolism.

The opposite is equally true. When the power of the brain to drive the

body to fabricate heat is impaired in shock, with each degree of the consequent fall in body temperature, the chemical activity of the organism is *diminished* 10 per cent., and there is a corresponding diminution of electric conductance. Therefore when, in a case of shock, heat is applied to the body, the rise in temperature produced by the external heat automatically increases the rate of production of internal heat ; in other words, the external heat not only assists the body by supplying heat from without, but also by enabling the enfeebled powers of the body to create more heat within itself.

For more than a century, surgeons have appreciated the value of increased body heat in shock ; of increased local heat in acute infection.

Rest and Sleep.—Because rest and sleep are as commonplace as water and oxygen, they are taken for granted. The researches of others, and our own, have shown that rest and sleep are as much a part of the biologic cycle of work and restoration as night is a part of the cycle of the day. There is no continuous day ; there is no continuous consciousness. Work and fatigue and restoration, translated into bio-electro-chemical terms, mean electric discharge, polarisation, and recharge. An electric battery, when weakened by too much work in the form of continuous or sudden complete electric discharge, is not restored by more and violent work. The human mechanism in shock or exhaustion is not restored by physical injury, nor by strychnin, nor by alcohol, nor by anesthetics, nor by camphor oil, nor by being made anxious, nor by painful examinations, nor by rough handling, but by rest and sleep, and by aiding the failing functions of organs.

Our best results will be secured if we understand the principles in accordance with which the biologic system operates. We shall then use the means sanctioned by evolution and survival, and never violate these simple principles. Let us first employ food and water, warmth and shelter, oxygen and rest and sleep—until we have found out how to do for the organism what sleep and other minor forms of negativity accomplish.

II. Hypothetical Effect of Exposure of Raw Tissue to the Air

The following considerations would more appropriately be designated a mere speculation.

AMPUTATIONS

Surgeons have always known that the higher the amputation of the leg and thigh, the higher the mortality rate ; that if more than one-third of the surface of the body is denuded of its skin, death will probably occur ; that the wider the dissection, the greater the exhaustion and shock. Especially is

this true of the division of muscles, as in high amputation of the thigh and in amputation at the shoulder. Among the factors that contribute to exhaustion and shock, we recognise the primary value of the vast number of traumatic afferent impulses entering the brain. These inflowing impulses may of themselves be sufficient to cause death.

That the high mortality of thigh amputations may be explained by the electro-chemical theory is inferred from the facts that blocking the spinal cord is all but specific in preventing shock; and that the use of nitrous oxid is almost equally protective.

In what manner does the division of large areas of muscle or the exposure of large areas of other tissue cause so much exhaustion and shock? And how are exhaustion and shock prevented either by nerve blocking or by nitrous oxid anesthesia?

In accordance with the electro-chemical conception, the blocking of the spinal cord protects the brain-cells against the impact of the incoming stimuli; and nitrous oxid, while it does not prevent traumatic stimuli from reaching the brain-cells, does prevent the full response of the brain-cells by diminishing oxidation within them. In either case there is a physiologic protection.

Despite these measures, however, in some cases there occurs later a considerable degree of shock. The electro-chemical theory supplies the following interpretation of this deferred shock:—Muscle-cells are concentration cells. The interior of each cell contains an accumulation of negative ions, which are retained within the cell by the membranes, which are impermeable to negative ions. When the cells are divided, therefore, these negative ions are released and a galvanometer will receive the current resulting from their escape. The exhibition of this current on the division of frog muscle is a standard experiment for medical students. Physiologists tell us that all living tissue, when divided, exhibits this 'current of injury.'

On the premises established by physical chemists, one would expect that the division of masses of muscle would release much kinetic energy in the form of the electricity which is supposed to drive the body. Nitrous oxid, by diminishing the creation of electric energy, conserves; nerve blocking may conserve by blocking the efferent current, as well as the afferent. The foregoing explanation is in harmony with the earlier conclusions in this volume, and with the fact that nerve blocking, nitrous oxid anesthesia supplemented by the immediate covering of the raw area with a non-conductor, and the use of heavy narcotisation by morphin, which blocks brain-cell metabolism—plus vast quantities of water—diminish the probability of death from shock in amputations of the thigh.

EXPOSURE OF ABDOMINAL VISCERA

Among the surgical mysteries has been the fact that the mere exposure of the abdominal viscera to the air causes exhaustion and shock. In accordance with the electro-chemical theory, one would suppose that in addition to the damage to the brain-cells produced by the afferent impulses there might be also a damaging loss of electric energy in the 'current or currents of injury.' That a certain degree of probability is attached to this conception is suggested by the following facts :—

(1) Nitrous oxid, which presumedly prevents the fabrication of electric energy by the brain-cells, almost specifically prevents shock from trauma or exposure of the abdominal viscera.

(2) In 'spinal animals,' that is, animals whose spinal cords have been severed several months previously, in which the efferent currents as well as the afferent are blocked, there is also almost a specific prevention of shock from trauma or exposure of the abdominal viscera.

(3) The time factor in the production of abdominal shock obeys a law which applies also to the loss of electric energy through the 'current of injury.' Roughly speaking, the degree of exhaustion is proportional to the area of exposed tissue multiplied by the intensity of trauma and by the length of exposure.

EXPOSURE OF TISSUE

(1) In our experiments on animals under complete anesthesia, shock was produced when the greater portion of the skin was removed ; and when extensive divisions of muscle were made.

(2) Merely exposing the fourth ventricle to the air causes a very great fall in the blood-pressure. Is this exhaustion due to a 'current of injury'?

(3) The exposure of large areas of the brain tissue soon leads to exhaustion.

On the other hand, in extensive burns, the toxic factor from partially decomposed proteins largely clouds the picture. In these cases, is it possible that the good effect of the covering with oil is wholly unrelated to the 'non-conductor' property of the oil ?

Multiple war wounds, whose individual areas make a large total of naked tissue, involving only the skin and subcutaneous tissue, have been attended by considerable, even fatal shock and exhaustion. Could these fatal results be due in part to the loss of electric energy, added to the 'drive' of the afferent impulses from the injury and the operation ?

NATURAL PROTECTION

The foregoing suggestions raise this pertinent question :—Is the surrounding air a good or a bad conductor ? The skin of man is a poor conductor. There is almost no conductance between dry air and the skin. Air itself is a poor conductor, and its conductance is dependent on its moisture. Dry skin is an exceedingly poor conductor. An oily skin is still less a conductor. Wool and hair and feathers are poor conductors. It would seem that the bio-electric mechanism of man and animals is encased in a fairly efficient non-conducting envelope. As suggested by Robertson,[1] possibly this explains the comfort of the 'bipped' wound with its non-conducting paraffin covering. May it not be possible that the physical depression produced by a humid day, or wet clothes, by wet and muddy environment, as in the trenches, is in some way related to the loss of energy through the increased conductance of damp air and a wet skin ?

III. The Shockless Operation through Anociation

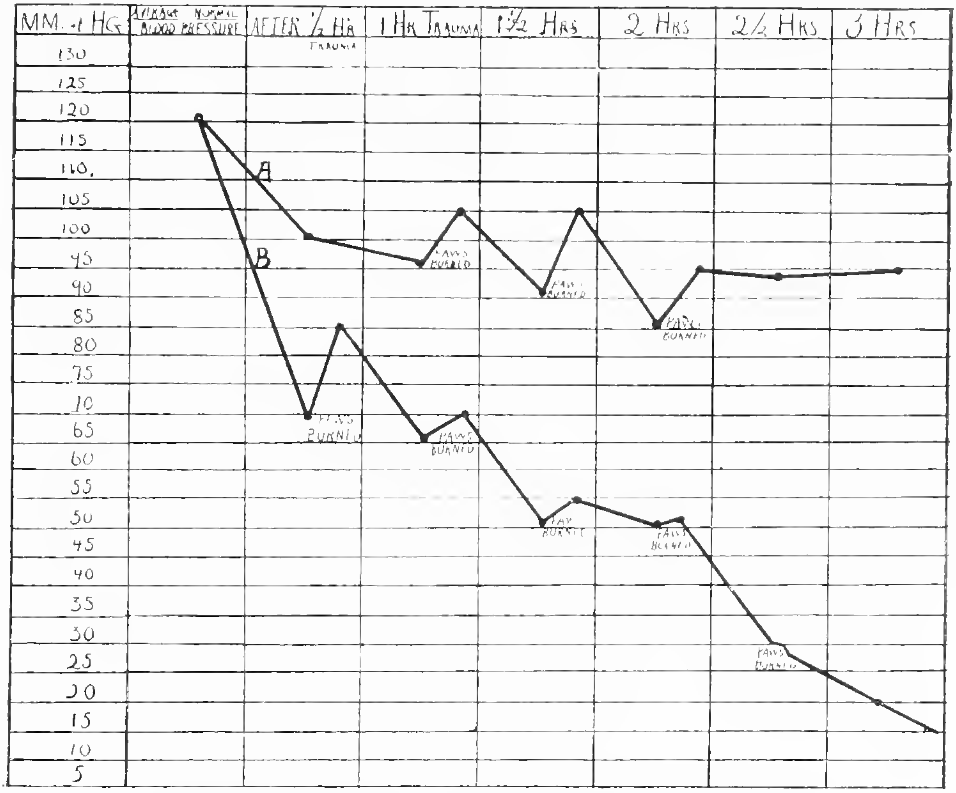
FUNDAMENTAL PRINCIPLES

(1) *Nitrous Oxid-Oxygen Anesthesia.*—Nitrous oxid-oxygen produces a light anesthesia and gives less muscular relaxation than ether or chloroform. *Special training in its administration is absolutely required*, for it is technically the most difficult of all anesthetics to administer safely. These disadvantages, however, are far outweighed by its advantages, as compared with ether or chloroform. It is quick in its action ; is pleasant to take ; recovery is immediate ; it produces but slight nausea ; it is protective—strongly protective —against the shock of operation. Nitrous oxid is almost a specific against shock (Fig. 113). It apparently owes this property to its interference with the use of oxygen by the brain-cells. In this sense, nitrous oxid is an ideal anociator ; to some extent it is as protective as the local blocking of nerves. Local blocking prevents the injuring stimulus from reaching the brain ; nitrous oxid permits the stimulus to reach the brain but minimises the response of the brain-cells, and to that extent prevents the exhaustion of the brain-cells.

Nowhere have the results of the use of nitrous oxid-oxygen been more dramatic than in military surgery in the front area. In a personal communication Major Gregory Marshall reported—and his report is typical—that in any

[1] Robertson, A. W. : *Studies in Electro-Pathology*, 1919.

series of grave cases in military surgery, the use of nitrous oxid alone will increase the recovery rate of abdominal and chest cases from 25 to 50 per cent., and of high amputations of the thigh 200 per cent., over the recovery rate of like cases operated upon under ether or chloroform.



Composite Tracings—A, Nitrous Oxid (plus Oxygen). B, Ether.

Fig. 113.—Protective Effect of Nitrous Oxid as Manifested by the Maintenance of Blood-Pressure in the Presence of Repeated Trauma, Compared with the Loss of Blood-Pressure in an Animal Subjected to Like Trauma under Ether.

For minor operations, nitrous oxid produces a pleasant analgesia in which pain is abolished while consciousness is retained. It can be given under positive pressure when desired. This is of especial benefit in chest operations, because it will maintain the lung flabbily within the chest against the chest wall, or protruding out of the opening in the chest wall, as may be required. It causes neither bronchitis, pneumonia, nor nephritis, and the patients recover so quickly that they can eat and drink soon after the operation. In the case of one patient, Gwathmey has given nitrous oxid-oxygen 139 times and neither tolerance nor dread was established.

Nitrous oxid, like ether and chloroform, must be pure. The apparatus for its administration must be capable of delivering any desired pressure and mixture of nitrous oxid-oxygen. The induction of anesthesia must be gradual, not too rapid, and respiration must be established and maintained at an even rate. The patient must be kept pink throughout the anesthesia. *The pink patient cannot die.* If complete anesthesia cannot be secured by nitrous oxid and oxygen alone, as in alcoholics, and there is difficulty in keeping the patient pink, or if anesthesia is attained but not sufficient relaxation, ether must be added. The safety of nitrous oxid-oxygen anesthesia is indicated by the fact that in one American clinic it has been administered by the chief anesthetist and the pupils of the clinic over 25,000 times without an anesthetic death.

Because nitrous oxid-oxygen anesthesia is more difficult to administer, costs more, and requires more expensive apparatus than ether, this anesthetic seems less satisfactory to the operator; but because its protection is so great, its inhalation so pleasant, its after-effects so slight, it must be regarded as strictly the patient's anesthetic.

(2) *Short, Deft Operation.*—The surgeon too often becomes so preoccupied with the technic and the purpose of the operation, that he forgets that he is cutting, retracting, or pulling living and exquisitely reactive tissue; that he is inflicting needless injury. He forgets that every moment the operation is prolonged beyond the actual requirement is a moment of unnecessary injury to an unconscious fellow-man, who has no means of protest, no means of defence, against a well-meaning, if certain, surgical execution. Therefore the surgical objective should be achieved by as short, as deft, as precise technic as is consistent with accuracy.

(3) *Local, Regional, or Spinal Anesthesia.*—Major Marshall's observations show that one of the immediate effects of *spinal anesthesia* is the fall in blood-pressure (Fig. 114). This has been conclusively shown in experiments on animals in our laboratory. Major Marshall has shown that the fall in blood-pressure is most severe in the patient whose blood is dilute, with low hemoglobin, and in the recently injured patient. When about forty hours or more have elapsed since the wound was received, spinal anesthesia is comparatively safe. This time corresponds with that required for stabilising the circulation by re-establishing the normal factors of safety. It is the recently injured man in deep shock that stands most in need of the protection of nerve blocking. In both the laboratory and clinic, it has been shown that shock cannot be caused by any amount of trauma upon an area physiologically severed from the brain by a local anesthetic, by blocking the spinal cord or the nerve trunks, or by local infiltration. In this manner, as far at least as trauma is concerned, a shockless operation may be performed, but the sights and sounds of the operating room, the patient's knowledge that his flesh is

being divided by a knife, that his blood-vessels are being divided and tied, the sound of the saw that severs his bones—all these contribute to psychic shock. Spinal anesthesia is therefore of value, provided that the consequent great fall in blood-pressure may be prevented and that the psychic factor may be eliminated by the technic of Colonel Hugh Cabot. Colonel

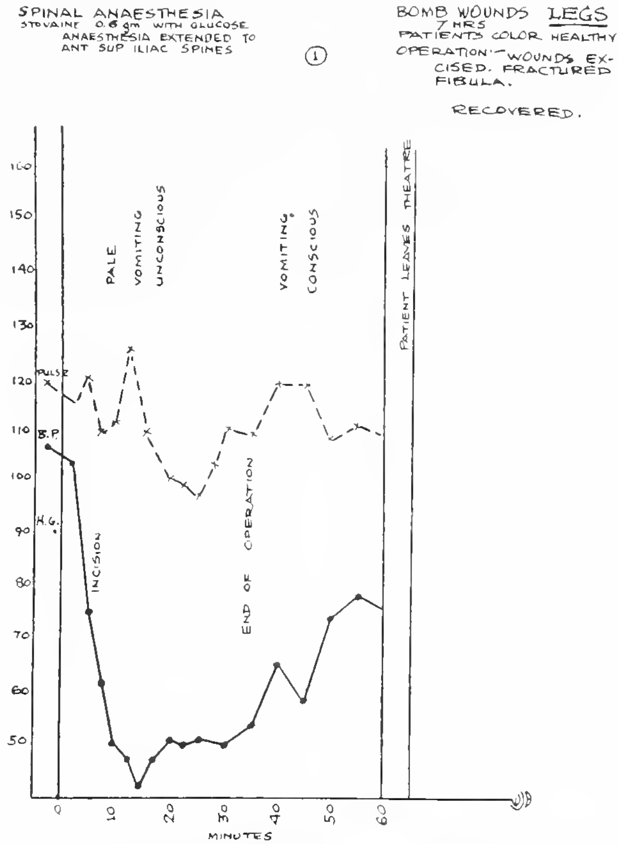


Fig. 114.—Fall in Blood-Pressure Caused by Spinal Anesthesia. (Courtesy of Major Gregory Marshall.)

Cabot injects 2 cc. of a 5 per cent. solution of novocain with adrenalin diluted with 2 cc. of spinal fluid, between the fourth and fifth lumbar vertebræ. At this level, the splanchnic area is not so markedly affected and the blood-pressure falls but slightly. Colonel Cabot reported to the author a series of 180 amputations of the thigh—90 under ether and 90 under spinal anesthesia. In this series the mortality rate of operations under spinal anesthesia was

50 per cent. below the mortality rate of operations under ether. Local anesthesia, when applicable, is excellent. When local anesthesia is used, it is best to give morphin or omnopon in advance.

(4) *The Shockless Operation.*—The practical application of the foregoing principles yields the shockless operation. This point has been securely established not only in the civilian but also in the military clinic, as is attested by the following statement by General Bowlby:[1] 'Its use (nitrous oxid oxygen) saved many lives, and in abdominal operations the very best results of all were obtained by combining it with infiltrative anesthesia of the abdominal wall. By this combined method the gas and oxygen required was reduced to a minimum, and the operator was not troubled by abdominal rigidity. It was by the use of this combination that Majors D. Taylor and G. Marshall at "Rémysiding" succeeded in saving 74 patients in a consecutive series of 101 operations for perforating wounds of the abdomen, and I believe that these results were the best obtained in the British Army during the war.' The following conditions yield the shockless operation:—

(*a*) The control of fear and anxiety, if not by management, then by a moderate dose of morphin.
(*b*) The use of nitrous oxid-oxygen anesthesia.
(*c*) Regional blocking by local anesthesia.
(*d*) A feather-edge technic.
(*e*) Keeping raw tissues covered as much as possible.
(*f*) Prevention of loss of blood.
(*g*) Prevention of loss of body heat.

These conditions can best be achieved only by a highly co-ordinated group—surgeons, assistants, nurses, and orderlies. The special problems at hand and the opportunity are factors which must be controlled by the surgeon.

There is one point that cannot be reiterated too often—the patient under ether anesthesia is in no way protected against shock. Tissues, for their own sake and in the interests of the entire organism, must be injured only to secure a net profit. The baneful effects of low blood-pressure must not be forgotten, and timely transfusion of blood is imperative.

APPLICATION OF THE PRINCIPLES OF ANOCIATION IN SPECIAL GROUPS OF CASES

Abdominal Operations

(*a*) If nitrous oxid is used, and *it is the anesthetic of choice*, use local infiltration also, to promote relaxation of the abdominal muscles. If relaxation is not complete, *during exploration*, add ether.

[1] Bowlby, A.: *Surg. Gyn. Obst.*, 1920, xxx. 13-21.

(*b*) If ether is employed, use Gwathmey's warmed vapour method. Employ local infiltration also, so that the least possible amount of ether will be used.

(*c*) If there is free blood, as in military surgery, Major Taylor's plan of leaving the blood in the abdomen until the intestinal technic is completed seems sound. Apparently, the free blood serves as a measurable protection against damage from the exposure to air.

(*d*) Turn a shock patient from side to side as little as possible during operation. (Major Gregory Marshall.)

(*e*) The abdomen must be kept open the least possible length of time.

(*f*) Manipulations and exposure of the viscera must be reduced to a minimum ; therefore, make an ample incision.

(*g*) If a patient is in deep shock, transfuse some blood at the beginning and more at the close of operation.

(*h*) In certain cases, if debility is marked, and the operation is such as to interfere with the physiologic balance of the patient—as in resections of the stomach, intestines, or gall-bladder—it is advisable to perform the operation in two seances, the second major step being taken after the nutritional balance is well established.

(*i*) In starved cases from cancer or in grave risks, nitrous oxid may be used only to provide analgesia, and anesthesia secured mainly by local anesthesia.

(*j*) If, as we believe, the liver is the key to chemical stabilisation, and if the chemical activity is increased by heat, then heat applied to the entire abdomen both before and after operation in bad risk cases, would increase the temperature of the liver, thus increasing its metabolism. This increased metabolism of the liver, in turn, would defend the organism as a whole. Thus far the clinical experience seems to bear out this assumption.

Operations on the Chest

(*a*) If there is cyanosis, give oxygen under pressure, with enough nitrous oxid for analgesia, until the gray-blue color, or the ordinary cyanosis, gives way to a pink color. It usually requires from ten to fifteen minutes for restoration of the internal respiration. When a pink color is restored, then give surgical anesthesia.

(*b*) Make an adequate exposure. Resecting a rib is better than working in a cramped space.

(*c*) Handle the lungs and heart and pleura precisely and gently, and *quit* when finished.

(*d*) Move the patient as little as possible.

(*e*) Close the chest air-tight.

(*f*) Give oxygen under pressure at intervals during the first twenty-four hours if required.

Operations on the Extremities

(*a*) When dealing with fractures, under anesthesia, no less than without anesthesia, the limb must be orientated and handled so skilfully that little or no crepitus will be felt.

(*b*) In amputations, divide the nerve trunks as lightly as possible, and handle the limb as little as possible.

(*c*) In grave shock, if no nitrous oxid is available, consider using low spinal anesthesia by Cabot's method, and be prepared to give blood transfusion to overcome the lowered blood-pressure caused by the anesthesia.

(*d*) We should not forget that the anesthetised patient is living, and responds to injury as readily as the unanesthetised.

(*e*) Cover and protect large wounds as much as possible.

Gassed Cases in Military Surgery

(*a*) First give oxygen under pressure, with just sufficient nitrous oxid to eliminate the worry due to the mask and to the oxygen inhalation.

(*b*) After the pink color is restored, give light surgical anesthesia.

(*c*) Make a short, deft operation.

(*d*) When required, give oxygen under pressure during the post-operative period.

(*e*) Local, regional, or spinal anesthesia is preferable to general anesthesia.

Hemorrhage

(*a*) If hemorrhage is critical and continuous, give enough blood transfusion to make anesthesia safe.

(*b*) Anesthetise.

(*c*) Secure the bleeding vessel.

(*d*) Transfuse enough blood to make up the normal quantity.

(*e*) Operate as little and as lightly as possible, for the anemia from the hemorrhage causes much damage to the vital organs and the normal resistance of the vital organs is reduced. Patients are not as strong after blood transfusion as they appear to be.

Acute Bounding Infections

(*a*) Deep narcotisation with morphin, and, if time permits, 1000 cc. of normal saline subcutaneously before operation.

(*b*) Nitrous oxid-oxygen anesthesia.

(*c*) ' Touch-and-go ' operation.

(*d*) Continuous morphin narcotisation for twenty-four hours or more until the patient is safe.

(*e*) *During morphin narcotisation*, always give saline subcutaneously, from 2000 to 3000 cc. each twenty-four hours.

(*f*) Give 5 per cent. sodium bicarbonate per rectum by the Murphy drip.

Prolonged Infections

(*a*) Transfusion of blood.

(*b*) Light, short operation.

(*c*) A second transfusion, if required.

(*d*) Sodium bicarbonate per rectum by the Murphy drip.

Ashen-Gray and Cyanosed Patients

Except in chest cases, in which there is gross defect in exchange of air, an ashen-gray or tallow-candle facies expresses so complete a failure of the internal respiration that the patient usually dies.

The one hope is to force oxygen under pressure in order to improve the internal respiration, and to give blood transfusion, if available ; if not, give Bayliss' gum infusion in the hope that internal respiration will become established in the vital organs. Unless the patient remains pink, it is of no use to proceed further. Many of these cases are influenced by nothing—they are potentially dead.

Exophthalmic Goiter

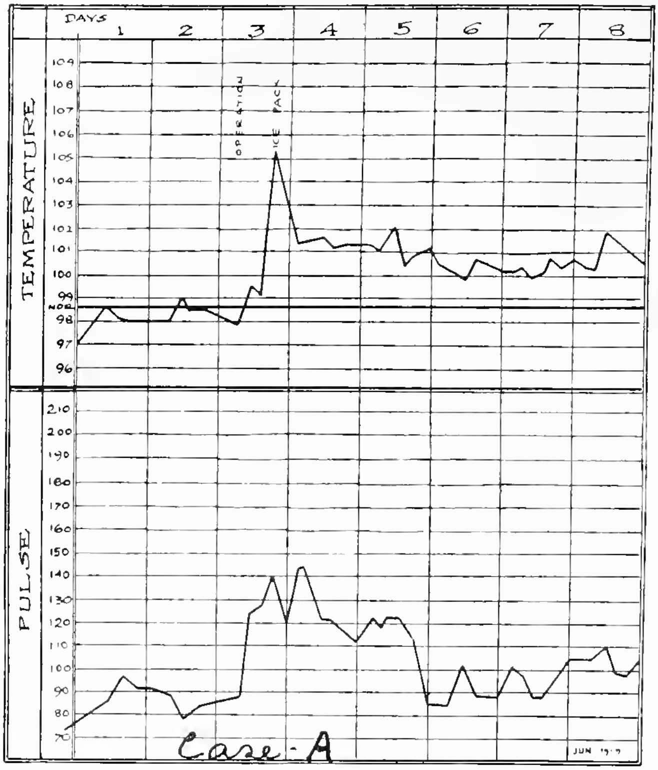
(*a*) In advanced exophthalmic goiter, the internal respiration is abnormally sensitive, as indicated by the adrenalin test (Goetsch), and by the baneful effect of diminished exchange of air as a result of emotion or of injury. The operative procedure should be graded according to the severity of the disease.

(*b*) The anesthetic should be nitrous oxid, which, as a rule, should be administered in bed, the patient being transferred to the operating room after anesthesia is established.

(*c*) In moderate cases, the entire operation may be completed at one seance.

(*d*) In more severe cases, diminish the thyroid activity by a preliminary ligation in bed, under nitrous oxid analgesia and local anesthesia.

(*e*) In extremely grave cases, it may be necessary to diminish the thyroid activity by multiple steps—boiling water injections (Porter) ; ligation of one vessel ; ligation of the second vessel ; partial lobectomy ; complete lobectomy ;



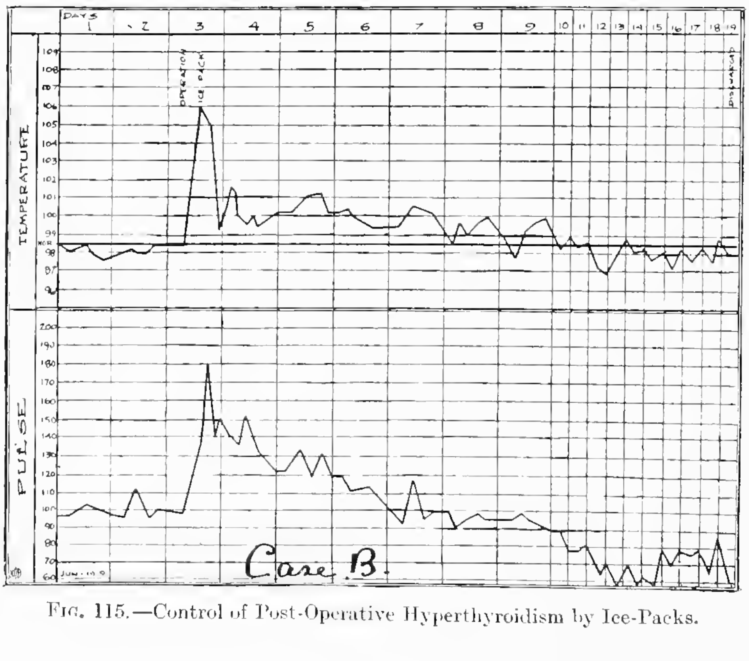


Fig. 115.—Control of Post-Operative Hyperthyroidism by Ice-Packs.

allowing intervals of a month or more between the successive stages as the condition of the patient may indicate. If, during operation, the pulse runs up beyond the safety point, stop the operation and dress the wound with flavine, and complete the operation after a day or two, when conditions are safe. In some cases, though the thyroid is resected, it is advisable to dress the unsutured wound with flavine and make a delayed closure in bed the following day under analgesia.

(*f*) In multiple stage operations, the length of interval is determined by the degree of physiologic adjustment.

(*g*) In certain cases, lobectomy is performed in bed under nitrous oxid analgesia and local anesthesia.

(*h*) Psychic control is required throughout to diminish the intense drive by establishing confidence and hope. An anociated regimen should be prescribed for the pre-operative, inter-operative, and post-operative periods.

(*i*) If after operation there is inaugurated an excessively high temperature, with greatly increased pulse and respiration, then, on the principle that heat increases chemical activity and electric conductivity, and that these in turn increase heat, such patients are literally packed in ice—packed early. This procedure has been found to exercise a remarkable control over the destroying metabolism. (Fig. 115.)

This post-operative phase of exophthalmic goiter is closely analogous to heat-stroke in symptoms and in control; and both heat-stroke and the so-called post-operative hyperthyroidism are the antithesis of shock in which by contrast the heat centre is paralysed. In the latter, heat is as useful as cold is in the former. The treatment for each is planned in accordance with the simple laws of physics. The practicability of the plan of treatment outlined above has made possible in the Lakeside Clinic the following record:—206 consecutive thyroidectomies, of which 126 were of the exophthalmic type, without a goiter death; 87 ligations without a death. The one death in the series was the result of double pneumonia. No case was rejected for operation.

IV. Limitations of Certain Methods of Treatment

Morphin

Except in chest wounds, do not use morphin in the presence of cyanosis.

Blood Transfusion

(*a*) In grey cyanosis, blood transfusion may fail.

(*b*) In progressive internal hemorrhage, blood transfusion may hasten bleeding.

(*c*) Too rapid introduction of blood in a patient with a weak myocardium may cause acute dilatation of the heart.

(*d*) If unmatched blood is given, especially in infection, serum reaction may occur. If matching of blood is impossible, transfuse a small amount and note the effect. Incompatibility can usually be discerned at once.

Spinal Anesthesia

(*a*) In the low blood-pressure of acute shock or hemorrhage, the additional fall due to spinal anesthesia as a result of the interruption of so large an area of vaso-motor nerves may cause dangerous, even fatal collapse. This may be prevented by blood transfusion.

(*b*) The psychic factor may be both distressing and damaging, but may be eliminated by morphin or by nitrous oxid analgesia, or by very light ether anesthesia.

(*c*) Occasionally spinal anesthesia is incomplete. Such a failure must be met by general anesthesia.

Nitrous Oxid

(*a*) In abdominal operations, muscular relaxation may not be complete under nitrous oxid anesthesia. This condition should be met by local anesthesia of the abdominal wall and by light handling.

(*b*) Nitrous oxid is a light anesthetic, demanding of the surgeon a light, deft operative technic.

(*c*) Nitrous oxid must be given only by *experts*; it is dangerous in *inexpert* hands.

Ether

(*a*) Ether tends to cause broncho-pneumonia, especially in abdominal operations during the winter.

(*b*) It diminishes, even temporarily abolishes, phagocytosis, and is therefore unsuitable in infections.

(*c*) There is a tendency to a fall in blood-pressure after operation; hence, it is unsuitable in shock.

(*d*) Ether causes a rather large diminution in the reserve alkalinity of the blood.

Saline Infusion

(*a*) If an excessive amount of saline solution is given intravenously, it accumulates excessively in the abdominal viscera.

(*b*) A greater amount of water is retained in the body when it is absorbed by mucous membranes or given subcutaneously.

Other Agencies

Strychnin, alcohol, digitalis, camphor, counter-irritants have been discarded.

V. The Acute Infections

The principles enunciated in preceding chapters suggest the following interpretation and treatment of the fulminating infections, such as spreading acute peritonitis, fulminating osteomyelitis, violent wound infection, etc.

The changes in pulse, temperature, and respiration indicate the intensity of the defence which the organism is making against the invading infection.

If the organism made no defence, it would perish; on the other hand, if the organism made a sufficiently excessive defence, it would commit suicide in the effort to prevent the invading micro-organism from destroying it. An animal may run so hard in flight from its pursuer as to defeat itself. The organism of the individual in the midst of an acute infection is doing the equivalent of running a Marathon race. The first thing that is required, therefore, is to cut down the dangerously excessive speed to a point of safety, *but only in case there is danger of self-destruction.* As we have seen, the one drug that has the power of control is morphin. Just as morphin limits the drive of muscular action and of emotion, to the same extent does it limit the drive of infection. The value of morphin in an acute phase of infection is not due to any influence on the bacteria, but to its action on the brain. Therefore, the greater the violence of the infection, the larger the dose of morphin. In critical cases, it should be administered in repeated quarter-grain doses until the respirations are reduced to ten or twelve per minute. In these cases, however, it must be remembered that morphin interferes with the secretion of many glands; it tends to desiccate the tissues at a time when large amounts of water are demanded. Therefore, when deep narcotisation with morphin is employed—*which is only in critical cases*—large amounts of water are demanded, for a double reason,—first, because the raging metabolism of the fever demands a corresponding increase in water; second, because morphin itself occasions the need of more water. In peritonitis, we usually give by Murphy drip as much of a 5 per cent. solution of sodium bicarbonate with 5 per cent. glucose as the bowel will absorb; and, in addition, we give subcutaneously from 2000 to 3000 cc. of normal saline each twenty-four hours during morphin narcosis. As long as water is given by the mucous membranes or subcutaneously, there is little danger of giving too much. By the combination of morphin to cut down metabolism, and water to facilitate elimination, the organism is remarkably safeguarded. In peritonitis, or in other acutely

grave infections, the morphin-water treatment rarely is required longer than forty-eight hours.

Prolonged Infections.—In the prolonged infections, morphin is contra-indicated. It is indicated, in fact, as a rule, for only one or two days in the dangerously severe, acute state. In prolonged infection, another set of problems arises.

(*a*) The metabolism is higher than normal.
(*b*) The appetite is usually impaired.
(*c*) In consequence of the above, there ensue emaciation and anemia, discouragement, restlessness, insomnia.

These states may be minimised, if not prevented, by putting these cases under the dietetic treatment of tuberculosis. Allow the patient to live in the open, *e.g.* on the veranda, on the lawn, in front of open windows. The monotony may be broken by removing the patient to another ward or to another part of the same ward, by diversion, by inspiring hope and confidence. If the body weight is not maintained, a therapeutic transfusion of blood may be given and repeated if needed. This treatment has produced remarkably good results in many cases. The value of transfusion is not necessarily due to the fact that it makes good the loss of blood by hemorrhage, or that it supplies the lack of hemoglobin in the secondary anemia ; but the 'boost' given by the new blood increases the internal respiration, which in turn increases the power of the electro-chemical mechanism, as is demonstrated in the patient by his increased confidence, his gain in strength, his sounder sleep, his increased appetite. Transfusion puts the patient's 'leg over the stile.'

CHAPTER IX

SUMMARY

In this volume we have presented summaries of researches in the laboratory and in the clinic whereby we have attempted to arrive at a better understanding of the phenomena of activation, of exhaustion, and of restoration.

We have found that exhaustion may be produced by an excess of, no less than by the want of thyroid or adrenal or brain activity. We have found that loss of liver function, want of oxygen, want of cardiac power, want of normal vaso-motor action, of themselves, individually or in any combination, may predispose to or cause exhaustion. We have found that excessive emotion, exertion, injury, infection, loss of sleep, hemorrhage, or the injection of acids, alike may cause exhaustion; and that, whatever the cause of exhaustion, certain basic phenomena are the same—muscular and mental weakness; diminished adaptive metabolism; increased respiration; increased pulse rate; sweating; diminished reserve alkalinity, and in acute phases, increased H-ion concentration of the blood; intracellular changes in the brain, the liver, and the adrenals; decreased electric conductance of the brain and increased electric conductance of the liver. We have found that *fundamental* restoration occurs only during rest and sleep, aided by such measures as secure quiet and comfort and reassurance; and that the processes of restoration may be aided by morphin, by heat, by fluids, and by measures that support and aid a failing mechanism, such as the proper ventilation of the lungs, and blood transfusion.

We have found that the acute exhaustion (shock) of surgical operations may be minimised or prevented by blocking the field of operation with local anesthetics, or by preventing the response of the brain-cells to the stimulus of traumatic impulses by nitrous oxid anesthesia.

We have concluded that the mechanism which produces the normal rhythmic alternation of consciousness and sleep is the mechanism whose alteration causes shock and exhaustion; and that in accomplishing restoration from exhaustion, this factor plays its part whatever the cause of exhaustion—whether emotion, exertion, physical injury, or infection, etc. We have concluded, moreover, that the action of this factor is governed by

the same law as that which governs the degree of exhaustion ; *i.e.* the degree of exhaustion produced by over-stimulation is proportional to the intensity of the stimulus multiplied by the duration of its application. This law holds true as well for the stimuli of normal untroubled consciousness as for the intense stimuli of acute infection or of extreme emotion ; for prolonged untroubled consciousness and short intense exertion or emotion alike produce exhaustion.

The cytologic phenomena, the 'time-multiplied-by-intensity' law, and the rhythmic alternation of consciousness and sleep—long rhythms for the centres governing voluntary activity, short rhythms for the centres of involuntary action —are in harmony with the hypothesis that electric energy is one form of kinetic energy into which the brain-cells transform their store of potential energy ; and that this electric energy mediates between the central electric batteries— the nerve-cells—and the end-organs, by means of whose activity adaptation is achieved. That is to say, by means of electric energy the nervous system drives the muscles and glands to perform the various physical and chemical activities by means of which the organism meets the vicissitudes of life.

Having thus glimpsed an electro-chemical theory, we have sought further evidence in its support. We have taken as our criteria in these investigations our histologic findings, which seemed to suggest that the concentration of electrolytes was altered as a result of excessive activation or lack of normal rhythmic restoration, and the theory that electric conductivity is a measure of vitality.

Of significance is our finding in experiments on rabbits that the conductivity of the cerebrum is higher than the conductivity of the cerebellum *except in the fetus* and the unconscious newborn, and in one instance in an unconscious patient, when this relation was reversed.

In processes leading to exhaustion, the altered conductivity of the liver is more marked and appears more promptly than that of the brain. This finding gave added significance to our earlier investigations, in which we found that excision of the liver is followed by a breaking down of the brain-cells, and that after decapitation, if life is maintained by the transfusion of blood and by artificial respiration, no histologic changes appear in the liver. These results, with the antithetic effects of exhaustion upon the conductivity of the brain and the liver, suggest that the liver plays a vital rôle in the function and the survival of the brain.

We infer that the cytologic changes in the brain-cells are the result of a change in permeability and of an intracellular acidosis. Biochemists have shown that all the cells of the body *except the brain-cells* possess within themselves means of protection against acidosis. In accordance with the electro-chemical theory it would seem reasonable to suppose that acids in

the brain-cell serve a rôle in the creation of electric energy comparable with the rôle of acids in the cells of a battery.

If the brain-cells constitute the driving electric battery of the organism, then they could not be hampered in their vital action by the presence of stores of inert matter for food or for protection against acidosis; and therefore the brain-cells depend for their protection upon the reaction of the surrounding fluids and the activity of other organs. We know that the liver, more than any other organ in the body, possesses the power of splitting up acid by-products. Therefore, as our histologic and conductivity findings have shown is the case, we would expect that the conductivity of the liver would vary with the general activity of the body, and that in exhaustion its cells would become changed in appearance and in conductivity.

It may be conceived that the function of the adrenal in the electro-chemical organism is that of a controller of oxidation. That the brain and the liver depend upon this function of the adrenals is indicated by the fact that adrenalectomy quickly produces in each the cytologic and conductivity changes characteristic of exhaustion.

Since the thyroid fabricates thyro-iodin, and since iodin increases permeability, it would seem that the vital relation of the thyroid to adaptive basic metabolism is the result of its influence on electric conductivity.

The practical test of the foregoing hypotheses is in progress in the crucible of the clinic. By the practical application of these conceptions in the Lakeside Clinic the mortality rate for bad risk patients has been markedly lessened and the range of operability extended. During the period between February 21, 1919, and April 23, 1920 (as this manuscript goes to press), the mortality rate of bad risk abdominal operations, including 32 gastro-enterostomies, 47 gall-bladder operations and 9 operations for cancer of the rectum, has been reduced to 1·2 per cent.

During the same period the mortality rate of 562 thyroidectomies has been 0·88 per cent.; this series including 300 thyroidectomies for exophthalmic goiter, with three deaths.

With such evidence of the practical value of bio-physical methods of attack upon clinical problems, it would seem that with the extension of physico-chemical investigations, medicine may approach a place among the exact physical sciences, and the physician may attack his problems from the more secure standpoint of the physicist.

ADDENDUM

Following the lead offered by the fact that with each degree of rise in temperature electrolytic conductivity is increased 2·5 per cent., since the preparation of this manuscript we have initiated a research to determine, if possible, to what extent the observed changes in electric conductivity, especially in the

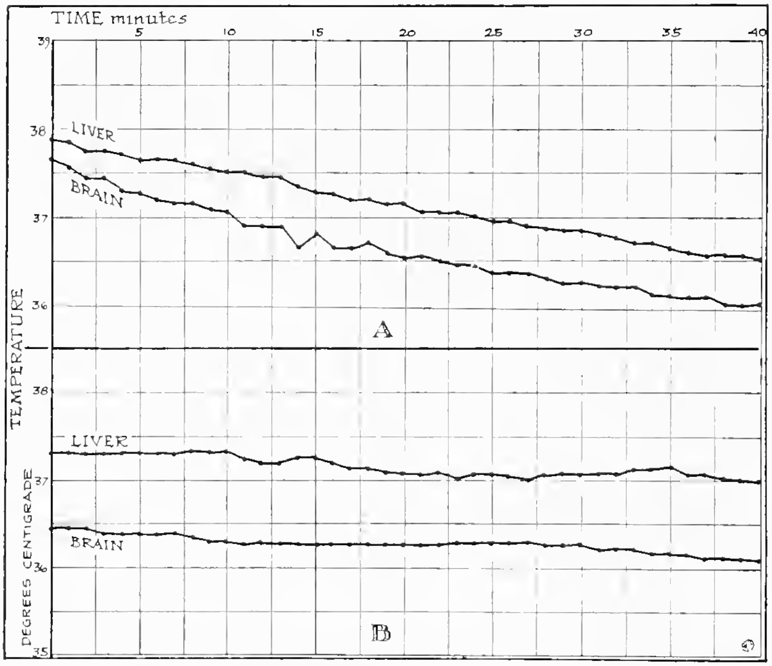


Fig. 116.—Comparison of the Effect on the Temperature of the Brain and Liver of A, Prolonged Ether Anesthesia; B, Prolonged Nitrous Oxid Anesthesia.

brain and the liver, have been attended by or have been the result of temperature changes. Thus far we have studied seventy-nine animals in which the variations in the temperature of the brain and of the liver under varying conditions have been measured by means of especially constructed thermo-couples. While the results of these preliminary studies are considered as tentative,

since they must be confirmed or disproved by greater refinements of technic, the following findings are so strikingly in accord with the findings in the previous researches heretofore summarised in this presentation, that we add the following supplementary notes :—

1. In two animals under ether anesthesia alone the temperature of the brain and of the liver declined steadily to the death point, and in all experiments under ether the tendency of the brain was toward a progressively decreased temperature. (Fig. 116 A.)

2. In two animals under nitrous oxid-oxygen anesthesia alone the tem-

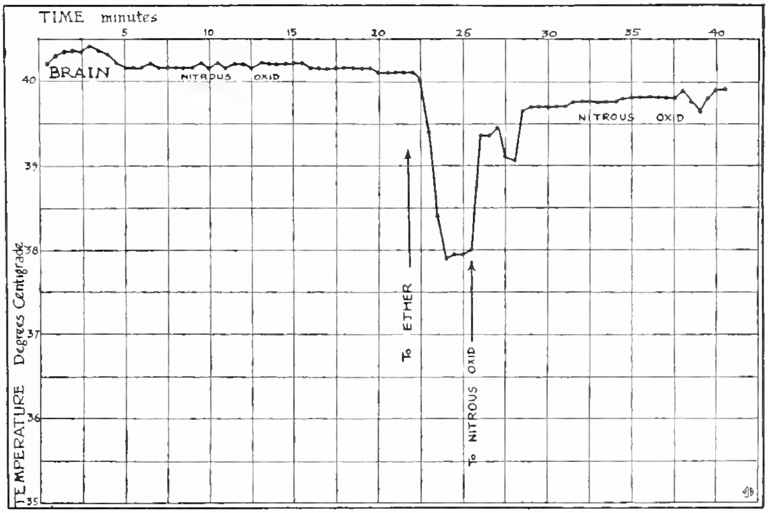


FIG. 117.—Comparison of the Effect of Nitrous Oxid and of Ether Anesthesia upon the Temperature of the Brain.

As indicated by the chart, after continuous nitrous oxid-oxygen anesthesia for twenty minutes, the nitrous oxid oxygen was discontinued and ether substituted. Upon the return to nitrous oxid the temperature rose to nearly its level before the change to ether.

Note the early rise in the temperature of the brain during the first five minutes of nitrous-oxid anesthesia corresponding with the period of excitement.

perature of the brain and of the liver was maintained at or near the normal level, and in all experiments under nitrous oxid oxygen but little change in the temperature of the brain was noted. (Fig. 116 B.)

3. In two normal conscious animals the injection of adrenalin produced a gradual rise in the temperature of the brain.

4. In animals under ether anesthesia in thirteen instances the injection of adrenalin produced a marked rise in the temperature of the brain. (Fig. 117.)

5. In animals under nitrous oxid-oxygen anesthesia in two instances the injection of adrenalin produced first a fall, followed by a slight increase in the

temperature of the brain; in three a slight and delayed rise; and in one instance the temperature of the brain remained unchanged. (Fig. 118.)

6. In two cases of acute iodism produced by the intro-peritoneal injection of iodoform, the temperature rise in the brain after the injection of adrenalin

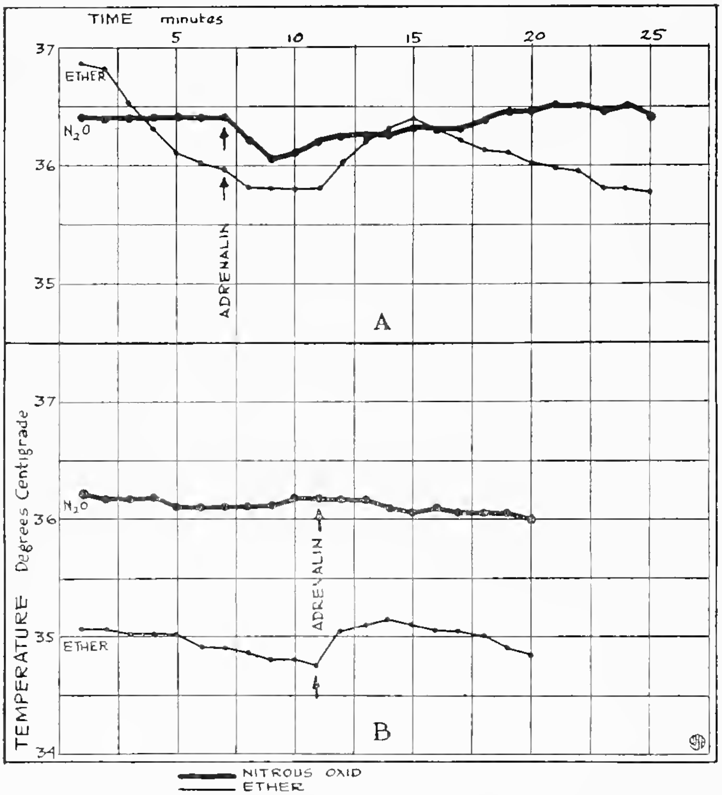


FIG. 118.—Effect upon the Temperature of the Brain of the Intravenous Administration of Adrenalin.

A, After short periods of ether and of nitrous oxid anesthesia
B, After prolonged ether and nitrous oxid anesthesia.

was greater and appeared more promptly than that produced by an equal dose of adrenalin in the brains of two normal animals.

7. In two experiments after adrenalectomy the temperature of the brain fell progressively until death, but the temperature of the liver fell but little below the normal point.

8. In two experiments after hepatectomy the temperature of the brain fell progressively to the death point, and the injection of adrenalin was followed by no change in the temperature of the brain.

9. In three animals which had been reduced to shock by exposure of the

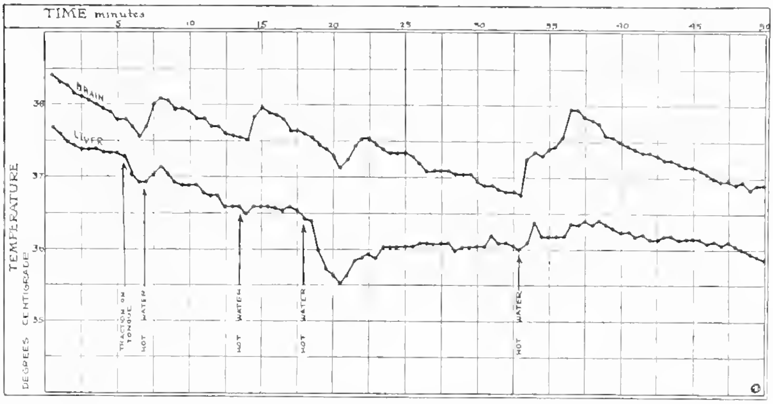


FIG. 119.—Effect upon the Temperature of the Brain of Injecting Hot Water into the Stomach.

In this animal after exposure of the intestines and shock-producing manipulations, hot water, 55° centigrade, was injected into the stomach by a tube passed through the mouth.

Note that in each instance the beginning of the increase in the temperature of the brain preceded an increase in the temperature of the liver.

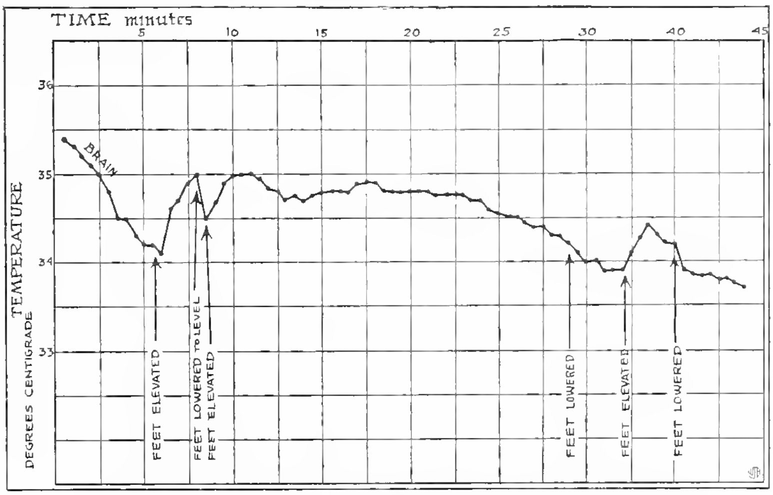


FIG. 120.—Effect upon the Temperature of the Brain of Elevating the Feet.

In this experiment the temperature of the brain was falling rapidly after hepatectomy when the animal was tilted head downward. The result, as shown in the chart, is in accord with clinical observations of the results of the head down posture and of blood transfusion.

intestines and shock-producing manipulations, the injection of hot water

into the stomach increased the temperature of both the brain and the liver, and the increase in the temperature of the brain seemed to appear more promptly than that in the liver. (Fig. 119.)

10. In two experiments on which animals had been reduced to exhaustion, one after hepatectomy, the other by exposure of the intestines and shock-producing manipulations, the elevation of the feet produced an immediate increase in the temperature of the brain. (Fig. 120.)

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